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COMPARATIVE EFFICACY OF VITAMIN D PREPARATIONS IN PROPHYLACTIC TREATMENT OF PREMATURE INFANTS

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THE NEED of the premature infant for vitamin D has generally been regarded as greater than that of the full term infant. It has been the common practice [1] to administer high doses of a concentrate of vitamin D as a measure of safety. Shelling and Hopper [2] and Gleich [3] suggested daily doses of 1,000 to 2,000 U. S. P. units. Indeed several reports [4] indicated that rickets may develop in premature infants even when 2,700 to 5,000 units of vitamin D is administered daily. Such dosages are in great contrast to that of 400 units which Stearns, Jeans and Vandercar [5] reported sufficient in full term infants for normal growth and prevention of rickets.

The recent discovery of vitamin D_3, formed by irradiation of 7-dehydrocholesterol, and the recognition of the probable presence of this compound in cod liver oil and in the skin of rats and swine has led to the commercial development of the compound for use in human nutrition. Though numerous reports appeared in which cod liver oil was compared with vitamin D_2 (as viosterol) in efficacy in allowing growth of infants and preventing rickets (the earlier reports were cited by Eliot

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1. Eliot, M. M., and Park, E. A.: Rickets, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1936, vol. 1, chap. 36.

2. Shelling, D. H., and Hopper, K. B.: Calcium and Phosphorus Studies: XII. Six Years' Clinical Experience with Viosterol in the Prevention and Treatment of Rickets, Tetany, and Allied Diseases, Bull. Johns Hopkins Hosp. **58**:137, 1936.

3. Gleich, M.: The Premature Infant, Arch. Pediat. **59**:5, 1942.

4. Davidson, L. T., and Merritt, K. K.: Viosterol in the Prophylaxis of Rickets in Premature Infants: Clinical, Chemical and Roentgenologic Observations, Am. J. Dis. Child. **48**:281 (Aug.) 1934. Malmberg, N.: Erfahrungen bei der Rachitisprophylaxe frühgeborener Kinder, Acta pædiat. **24**:375, 1939.

5. Stearns, C.; Jeans, P. C., and Vandercar, V.: The Effect of Vitamin D on Human Growth in Infancy, J. Pediat. **9**:1, 1936.

and Park [1]), no direct comparisons have been made of vitamin D_3 as such with vitamin D_2 in human subjects. Eliot and Park [1] concluded from an analysis of 39 reported investigations, as well as from their own experience, that "for practical purposes the vitamin D in viosterol may be regarded as being equal to vitamin D of cod liver oil." Even should cod liver oil prove to have some superiority over irradiated ergosterol in human nutrition, this superiority will not necessarily be due to the presence of vitamin D_3 in cod liver oil. It may be due to the presence of other beneficial substances or to the absence of harmful factors.

Two other forms of vitamin D have recently become commercially available. One of these is crystalline vitamin D_2, prepared by recrystallization of the product obtained by ultraviolet irradiation of ergosterol. This product has the theoretic advantage of being more nearly pure, thus avoiding any potentially harmful effects of by-products of irradiation. The second product is vitamin D_2 made by bombardment of ergosterol by electrons. The biologic as well as chemical similarity of this compound to irradiated ergosterol was demonstrated by McQuarrie and associates.[6]

It was the aim of the present investigation to determine, if possible, the relative efficacy of these several preparations as sources of vitamin D for the prevention of rickets and the promotion or allowance of growth in premature infants. Since such a comparison could not be made critically if optimal or excessive doses of vitamin D were administered, it became necessary to plan the study so as to determine at the same time the minimal requirements of vitamin D by these infants.

METHODS

Four preparations of synthetic oleo vitamin D U. S. P.[7] were used in these studies: (1) vitamin D_2 (American Research Products, Inc. process) prepared by low velocity electron activation of ergosterol; (2) viosterol, which is vitamin D_3 prepared by ultraviolet irradiation of ergosterol; (3) crystalline vitamin D_2, which also is prepared by ultraviolet irradiation of ergosterol and separated by recrystallization and (4) "delsterol" (vitamin D_3), prepared by ultraviolet irradiation of 7-dehydrocholesterol.

These products were furnished to us dissolved in corn oil in concentrations of approximately 200,000 U. S.P. units per gram. For administration to the

6. McQuarrie, I.; Thompson, W. H.; Stoesser, A. U., and Rigler, L. G.: The Antirachitic Potency of Ergosterol Activated by Low Velocity Electrons, J. Pediat. **10**:295, 1937.

7. The preparation made by the American Research Products, Inc., process was furnished by General Mills, Inc., Minneapolis, and is hereafter referred to as the A. R. P. I. vitamin D_2. Solution viosterol in oil was supplied by Mead Johnson & Company, Evansville, Ind.; crystalline vitamin D_2 was supplied by Winthrop-Stearns, Inc., New York, and "delsterol" (activated 7-dehydrocholesterol) was supplied by Distillation Products, Inc., Rochester, N. Y.

infants, these concentrated solutions were diluted with corn oil to produce a calculated strength of 1,150 units per cubic centimeter. This diluted solution supplied 800 units in 16 drops from specially standardized droppers of dropper bottles. During the stay of the infants in the hospital, 5,000 units of vitamin A in corn oil was given daily as a separate administration. For home use the vitamin D was prepared in corn oil containing vitamin A, so that the daily prescribed dose of vitamin D also contained 5,000 U. S. P units of vitamin A.

The diluted vitamin D preparations were biologically assayed in two independent laboratories according to the standard "United States Pharmacopoeia" methods. The first assays were made by the nutrition laboratories of General Mills, Inc., in Minneapolis, at the levels determined from the concentrations stated on the labels of the original products. The second assays were made by the Laboratory of Vitamin Technology, in Chicago, at the levels determined by the General Mills assays. These twofold assays were made at the beginning of the study and again almost a year later when the project was well on toward completion. The findings of the two laboratories in each assay agreed with each other within the limits of error of the biologic determination and necessitated only a slight correction of the original dilution.

All infants admitted to the premature station of the hospital were placed on the vitamin D project if they were not acutely ill and if they could take the routine feeding. (An infant was regarded as prematurely born if his weight at birth was less than 5 pounds [2,268 Gm.].) The aim was to study the effect of vitamin D on each infant for a period of eight months, the first one and one-half month in the hospital and the remaining six and one-half months in a specially prepared outpatient clinic. To avoid the possible inclusion of other sources of vitamin D in the diet, the infants were fed formulas made up from diluted evaporated cow's milk which contained no added vitamin D.[8] The diet was supplemented with 50 mg. of ascorbic acid during the period in the hospital. At home, orange juice was used as a source of this vitamin.

While in the hospital the infants were measured and weighed at least every week. Roentgenograms of the long bones were obtained at 2 weeks and 6 weeks. When the infant was discharged from the hospital, the mother was instructed to bring the baby to the outpatient clinic every two weeks, at which time she was to obtain free a two weeks' supply of evaporated milk and of the preparation of vitamins D and A, which was in a small dark bottle containing the standardized dropper. The infant was weighed, measured and carefully examined clinically at each of these visits by one of us (K. G.), assisted by two nurses especially assigned to this project. Roentgenograms were obtained every four weeks in the outpatient clinic by a special technician assigned to this project. Chemical analyses of the blood were made at least once for almost all the infants, and a number of times for each infant if suspicion of rickets developed.

The chemical analysis included determinations of hemoglobin concentration and serum inorganic phosphorus and serum alkaline phosphatase (Bodansky) levels by photoelectric methods described by Hoffman.[9] Serum calcium was determined by the macro oxalate method, in which 2 cc. of serum was utilized to minimize technical errors.

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8. Dean's Brand Homogenized Evaporated Milk, without added vitamin D, next was used throughout the study.

9. Hoffman, W. S.: Photelometric Clinical Chemistry, New York, William Morrow & Co., Inc., 1941.

Although more than 500 infants were placed on the project over fifteen months, only 166 could be followed for the full period of eight months. An additional 22 babies were studied for more than six months. Data on these infants are not included in the survey, except for the blood chemical values. The infants were placed on one of four dosages of one of the four vitamin D preparations. Thus, there were 16 categories: daily dosages of 100 units, 200 units, 400 units and 800 units for each of the four preparations. Though the plan of rotation was originally utilized, the unforeseen losses late in the study made the final distribution of infants far from even. However, the planned effort to make the number of infants in the 100 and 200 unit groups largest was successful.

Since the study covered a period of almost two years, the variation in potential exposure of the infants to sunlight could not be avoided. Obviously, the mothers could not be enjoined to keep the babies away from sunlight during the summer months. However the attempt was made to intensify the admissions to the project during the months between July and December and to make fewer admissions during the remaining portion of the year. Thus, a relatively small number of babies were under home care during the summer months, and it was arranged that the larger portion of these would be on the 400 and 800 unit dosages. It was felt, therefore, that, even though the survey could not achieve the desired accuracy in the control of exposure to sunlight, the inaccuracy was least involved in the 100 and 200 unit groups which were crucial to the study.

The daily caloric intake of the infants was eventually 120 calories per kilogram, but for the early weeks of their stay in the hospital it was much less because the volume and carbohydrate content of the diet were kept relatively low. The required calories were obtained by a dilution of evaporated milk with somewhat more than an equal quantity of water, to which mixture 5 Gm. of "dextri-maltose" was added. Additional water in the form of weak tea was offered between feedings. This diet was high in protein and minerals. After the baby was taken home, the milk formula prescribed was 13 ounces (390 cc.) of evaporated milk diluted to 1 quart (1 liter) with water, to which was added about 30 Gm. of "dextri-maltose." Eventually at about 3 months of age this quantity was the daily intake.

RESULTS

Incidence of Rickets.—The most important observation in the study was that no case of clinical rickets occurred in any of the groups. Apparently a dosage of only 100 units of vitamin D daily of any preparation was sufficient to prevent the flagrant signs and symptoms of rickets, in spite of the fact that the infants were prematurely born and that 85 per cent of them were Negro, both of which factors are known to favor the production of the disease.

In spite of the absence of clinical rickets, there was evidence or suspicion of rickets in 32 infants by the other criteria (see table 1). These criteria were (1) roentgenographic evidence of enlargement, cupping and fraying of the epiphysial lines, with or without some bowing of the shafts and (2) elevation of serum alkaline phosphatase concentrations. The upper limit of normal phosphatase levels for premature infants has not been well defined. Bodansky and Jaffe[10] gave 15

10. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: V. Serum Phosphatase as a Criterion of the Severity and Rate of Healing of Rickets, Am. J. Dis. Child. 48:1268 (Dec.) 1934.

TABLE 1.—*Incidence of Potential Rickets in 166 Premature Infants*

	A.R.P.I. Vitamin D_2, U.S.P. Units per Day				"Delsterol" (Vitamin D_2), U.S.P. Units per Day				Crystalline Vitamin D_2, U.S.P. Units per Day				Viosterol (Vitamin D_2), U.S.P. Units per Day			
	100	200	400	800	100	200	400	800	100	200	400	800	100	200	400	800
Total number of infants	15	12	12	9	14	10	6	7	16	5	11	8	11	7	13	10
Elevated phosphatase levels and negative roentgenographic signs	3	4	1	2	4	3	..	..	..	1	2	1	..	1	..	1
Elevated phosphatase levels and suspicious roentgenographic signs	2	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..
Elevated phosphatase levels and positive roentgenographic signs	..	..	..	..	1	..	1	..	1	..	1	..	..	..	..	..
Normal phosphatase levels and positive roentgenographic signs	..	..	..	..	..	..	..	..	..	..	..	1	..	..	..	2

Bodansky units per hundred cubic centimeters as the upper limit of normal for children. This level may be too low for premature infants, as will be discussed later, but it was used provisionally as a point of reference.

Three infants on 800 units of vitamin D (2 who received viosterol and 1 given crystalline vitamin D_2) showed signs of rickets on roentgenograms at about 5 months. These infants had shown no elevation in serum phosphatase nor any change in the serum calcium or phosphorus concentrations two months earlier. These signs were difficult to explain. They disappeared spontaneously and the serum chemical values remained normal, in spite of no increases in the dosage of vitamin D. If these signs represented true rickets, they may have been due to temporary neglect of administration or to interference with absorption of vitamin D or of calcium and phosphorus.

Roentgenographic signs suggestive of early rickets occurred in 4 other infants. Two of these subjects received 100 units of vitamin D daily (1 was given crystalline vitamin D_2 and 1 "delsterol"). Both had elevated serum phosphatase concentrations, the former having values ranging from 17.2 to 38.0 units per hundred cubic centimeters, the latter a value of 15.1. However, serum calcium and phosphorus concentrations were normal. The remaining 2 patients with positive roentgenographic signs received 400 units daily. One of these was receiving crystalline vitamin D_2; this patient had a serum phosphatase level of 28.2 units per hundred cubic centimeters at 26 weeks, which dropped to 12 units at 32 weeks and 8.8 units at 36 weeks without a change in the dosage of vitamin D. The other, who was given "delsterol," had a serum phosphatase concentration up to 41.3 units at 18 weeks, but this value dropped steadily, until at 34 weeks it was 1.4 units per hundred cubic centimeters. The patient receiving 400 units of crystalline vitamin D_2 had an obviously irresponsible mother who might not have faithfully administered the vitamin until the child's condition was seriously brought to her attention. The serum calcium and phosphorus concentrations were normal in this infant, but the child given 400 units daily of "delsterol" had a serum phosphorus level of 5.2 mg. and a calcium concentration of 8.2 mg. per hundred cubic centimeters at the time the phosphatase measured 41.3 units. Later, both phosphorus and calcium rose to normal.

Two other infants, who were receiving 100 units daily of A. R. P. I. vitamin D_2 had suspicious bowing of the long bones but no evidence of rachitic changes at the epiphyses. One had a serum phosphatase level of 23.1 units per hundred cubic centimeters at 24 weeks and of 19.2 units at 34 weeks, with normal calcium and phosphorus concentrations. The second had 16.3 units of phosphatase at 28 weeks but only 12.8 units at 32 weeks. The serum calcium and phosphorus concentrations were

normal. Thus, altogether roentgenographic evidence or suspicion of rickets occurred in 9 infants, in 3 of whom there were no corroborative serum chemical findings.

At some time 23 infants showed serum phosphatase levels above 15 units per hundred cubic centimeters without roentgenographic or clinical signs of rickets. Their distribution is indicated in table 1. Eight occurred in the 100 unit groups, 8 in the 200 unit groups, 3 in the 400 unit groups and 4 in the 800 unit groups. In all these subjects no abnormalities were observed in the concentrations of serum phosphate or calcium, except for a phosphate level of 3.9 mg. per hundred cubic centimeters in an infant receiving 400 units of crystalline vitamin D_2 and another of 4.8 in a baby receiving 800 units of A. R. P. I. vitamin D_2. In both these infants, the calcium concentrations were normal. It is significant that at least 15 of these 23 infants showed a return of serum phosphatase concentrations to values below 15 units per hundred cubic centimeters without any increase in the dosage of vitamin D. This observation would create some doubt as to the validity of utilizing 15 units per hundred cubic centimeters as the upper limit of normal, in spite of the fact that the greater incidence of values above 15 is where it was expected to be, in the 100 and 200 unit groups. If 20 units per hundred cubic centimeters were chosen as the upper limit of normal phosphatase concentration, the total incidence of elevated phosphatase levels (see table 2) would be 12, of which 10 were in the 100 and 200 unit groups, 2 in the 400 unit groups and none in the 800 unit group, which distribution was also to be expected.

Serum Phosphorus, Calcium and Phosphatase Levels.—The distribution of serum phosphorus, calcium and phosphatase values is shown in table 2. In this table, the lowest values determined in each group for serum phosphorus and calcium and the highest value for phosphatase were utilized. The averages of the phosphorus concentrations for the 16 groups ranged from 6.3 to 8.1 mg. per hundred cubic centimeters, with a total average of 7.3 mg. For each of the four dosages, irrespective of the type of vitamin used, the averages were almost identical. Similarly, no distinction could be drawn on the basis of the type of vitamin D administered if the dosage was ignored. It is to be noted that the average values for serum phosphorus were unusually high. Relatively few infants had phosphate levels below 7.0 mg. per hundred cubic centimeters; a considerable number had values above 8.0 mg.

Serum calcium concentrations showed averages for the various groups ranging from 10.5 to 11.8 per hundred cubic centimeters. The over-all average was 11.1 mg. Few values were below 9 and none below 8 mg. per hundred cubic centimeters. On the other hand, a considerable number of calcium concentrations were well above 11 mg. As in the case of serum phosphorus, no significant difference could be observed

TABLE 2.—*Distribution and Averages of Serum Inorganic Phosphorus, Calcium and Phosphatase Concentrations in Infants Receiving Various Doses of Vitamin D*

	A.R.P.I. Vitamin D_2, U.S.P. Units					"Delsterol," U.S.P. Units					Crystalline Vitamin D_2, U.S.P. Units					Viosterol, U.S.P. Units				
	100	200	400	800	All Dosages	100	200	400	800	All Dosages	100	200	400	800	All Dosages	100	200	400	800	All Dosages
Serum phosphorus, mg./100 cc.																				
7	7	3	5	3	..	5	6	2	3	..	4	2	4	2	..	2	2	0	2	..
7-8	8	4	4	4	..	3	3	2	2	..	7	3	4	7	..	6	4	4	4	..
8	5	6	3	1	..	3	2	7	2	..	5	1	1	2	..	3	2	2	0	..
Average (mg./100 cc.)	7.4	7.8	7.3	6.9	7.4	7.6	6.8	8.1	7.2	7.4	7.5	6.3	6.6	7.5	7.1	7.5	7.4	7.6	7.2	7.4
Serum calcium, mg./100 cc.																				
9	2	0	0	0	..	2	1	1	1	..	0	0	0	0	..	1	0	0	0	..
9-11	7	12	10	6	..	4	6	3	0	..	4	3	5	4	..	4	7	0	2	..
11	6	4	6	6	..	3	3	5	5	..	9	2	2	7	..	5	4	6	3	..
Average (mg./100 cc.)	10.9	10.7	10.9	11.1	10.9	10.5	10.7	11.3	11.2	10.9	11.8	10.8	10.6	11.7	11.4	11.1	10.8	12.2	11.5	11.3
Serum phosphatase, units/100 cc.																				
0-10	9	2	5	3	..	3	5	5	4	..	5	4	3	6	..	4	4	3	2	..
10-15	4	6	6	3	..	3	4	4	3	..	3	1	3	4	..	7	3	3	3	..
15-20	3	3	1	2	..	2	2	1	0	..	0	1	2	1	..	0	0	0	1	..
20-40	3	1	0	0	..	3	1	0	0	..	0	0	1	0	..	0	0	0	0	..
40	0	0	0	0	..	0	0	1	0	..	1	0	0	0	..	0	1	0	0	..

Averages for all subjects on 100 unit dosage: serum phosphorus measured 7.5 mg. and serum calcium 11.1 mg.; for all subjects on 200 unit dosage: serum phosphorus measured 7.2 mg. and serum calcium 10.7 mg.; for all subjects on 400 unit dosage: serum phosphorus measured 7.4 mg. and serum calcium 11.1 mg., and for all subjects on 800 unit dosage: serum phosphorus measured 7.2 mg. and serum calcium 11.4 mg.

For each group, the lowest serum phosphorus and calcium and the highest phosphatase levels were chosen.

TABLE 3.—*Average Gain in Weight by Two Month Periods for Premature Infants Receiving Various Dosages of Vitamin D*

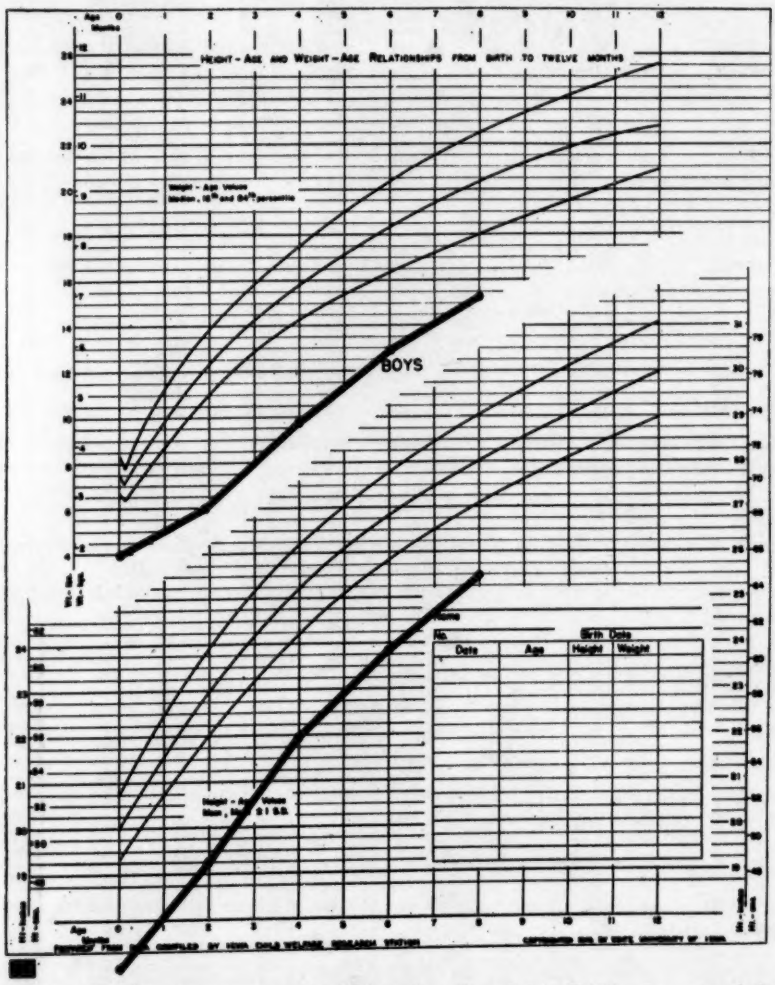
	Daily Doses, U.S.P. Units	Number of Infants	Grams Gained in Weight				
			0 to 2 Mo.	2 to 4 Mo.	4 to 6 Mo.	6 to 8 Mo.	Over-all Gain
A.R.P.I. vitamin D_2	100	15	17.3	28.0	23.2	15.1	20.6
	200	12	14.2	27.8	27.4	18.8	22.0
	400	12	13.6	34.7	26.8	19.7	23.4
	800	9	13.0	29.6	27.9	17.0	22.4
Total		48	14.8 Gm.	29.9 Gm.	26.0 Gm.	17.5 Gm.	21.9 Gm.
"Delsterol" (vitamin D_2)	100	14	13.2	25.9	25.0	19.4	20.9
	200	10	16.3	24.8	19.9	12.1	18.4
	400	6	16.4	30.7	25.6	18.2	22.2
	800	7	16.3	34.4	23.7	11.3	21.8
Total		37	15.1 Gm.	28.0 Gm.	23.5 Gm.	15.8 Gm.	20.6 Gm.
Crystalline vitamin D_2	100	16	12.5	29.3	25.0	17.5	21.4
	200	5	13.8	26.5	27.6	19.9	22.0
	400	11	19.3	26.0	26.1	15.9	21.9
	800	8	16.4	24.4	21.5	22.2	20.7
Total		40	15.2 Gm.	27.1 Gm.	24.9 Gm.	18.3 Gm.	21.4 Gm.
Viosterol (vitamin D_2)	100	11	14.1	30.9	29.0	21.1	23.4
	200	7	9.3	28.0	23.1	16.3	18.9
	400	13	12.4	25.6	24.9	19.2	20.9
	800	10	13.9	31.7	24.5	16.8	21.8
Total		41	12.7 Gm.	28.9 Gm.	25.6 Gm.	18.6 Gm.	21.5 Gm.
All infants		166	14.5 Gm.	28.6 Gm.	24.9 Gm.	17.6 Gm.	21.4 Gm.
Infants with evidence of rickets		32	15.1 Gm.	26.2 Gm.	24.3 Gm.	19.5 Gm.	21.1 Gm.

TABLE 4.—*Average Gain in Total Length by Two Month Periods for Premature Infants Receiving Various Doses of Vitamin D*

	Daily Dose, U.S.P. Units	Number of Infants	Centimeters Gained in Total Length				
			0 to 2 Mo.	2 to 4 Mo.	4 to 6 Mo.	6 to 8 Mo.	Over-all Gain
A.R.P.I. vitamin D_2	100	15	0.092	0.114	0.083	0.062	0.087
	200	12	0.089	0.114	0.080	0.056	0.086
	400	12	0.139	0.104	0.097	0.036	0.093
	800	9	0.090	0.114	0.103	0.025	0.085
Total		48	0.103 cm.	0.113 cm.	0.090 cm.	0.048 cm.	0.088 cm.
"Delsterol" (vitamin D_2)	100	14	0.116	0.108	0.093	0.071	0.096
	200	10	0.122	0.090	0.060	0.070	0.077
	400	6	0.099	0.120	0.072	0.059	0.088
	800	7	0.102	0.091	0.081	0.070	0.085
Total		37	0.112 cm.	0.103 cm.	0.079 cm.	0.069 cm.	0.088 cm.
Crystalline vitamin D_2	100	16	0.082	0.098	0.092	0.059	0.084
	200	5	0.084	0.143	0.063	0.079	0.089
	400	11	0.100	0.122	0.064	0.078	0.086
	800	8	0.091	0.114	0.047	0.078	0.084
Total		40	0.089 cm.	0.113 cm.	0.072 cm.	0.071 cm.	0.085 cm.
Viosterol (vitamin D_2)	100	11	0.114	0.098	0.092	0.061	0.089
	200	7	0.075	0.103	0.086	0.072	0.084
	400	13	0.098	0.101	0.079	0.075	0.088
	800	10	0.080	0.132	0.068	0.083	0.085
Total		41	0.093 cm.	0.108 cm.	0.081 cm.	0.073 cm.	0.087 cm.
All infants		166	0.099 cm.	0.110 cm.	0.081 cm.	0.064 cm.	0.086 cm.
Infants with evidence of rickets		32	0.100 cm.	0.098 cm.	0.089 cm.	0.068 cm.	0.086 cm.

between the calcium values of one group and those of another whether considered on the basis of dosage or on the basis of the type of vitamin D administered.

Table 2 also gives the distribution of phosphatase levels in 163 subjects. The arithmetical averages of these levels have not been calculated, for the occasional extremely high levels would distort the



Curves showing average growth in length and weight of 166 premature infants receiving the various preparations and dosages of vitamin D as compared with standard growth curves of full term babies as derived by Jackson and Kelly (*J. Pediat.* **27**:215, 1945).

averages of the groups in which they were found. The bulk of the values lay between 5 and 15 units, as was to be expected. The incidence of high phosphatase levels has already been considered in the previous section. Table 2 lists 31 cases of phosphatase levels above 15 units per

hundred cubic centimeters which include, in addition to the 29 previously discussed, 2 elevated levels found among the infants studied for only six months. These were 15.1 units for an infant receiving 400 units of "delsterol" and 15.4 units for an infant receiving 100 units of "delsterol." The total incidence of phosphatase levels above 15.0 units per hundred cubic centimeters was 19.0 per cent. For the several vitamin D preparations the incidence was as follows: A. R. P. I. vitamin D_2 25.5 per cent, "delsterol," 24.4 per cent, crystalline vitamin D_2 15.0 per cent, and viosterol, 6.4 per cent. If, however, 20 units per hundred cubic centimeters was chosen as the upper limit of normal, the total incidence of higher than normal values was 12, or 7.4 per cent. For A. R. P. I. vitamin D_2 the incidence of levels above 20 units was 7.8 per cent, for "delsterol," 10.0 per cent, for crystalline vitamin D_2, 5.0 per cent and for viosterol, 3.3 per cent.

Effect of Vitamin D on Growth.—Table 3 gives a summary of the increases in weight in the 166 infants on the various doses of the several vitamin D preparations. The average gain in weight per day of all the babies for the eight month period was 21.4 Gm. When the groups receiving the different vitamin D preparations are compared with each other, a striking similarity in the gains in weight is seen. Likewise, there is no significant difference in the gains in weight among the groups on the basis of dosage of vitamin D. In table 4 similar results are shown with respect to the gains in total length. No recognizable difference in the average gain in length for the infants receiving any vitamin preparation at any dosage level occurred. That the gains in weight and length were uniformly good and comparable to those of standard growth curves is shown in the chart.

COMMENT

The data reported point to one significant conclusion: that is, dosages ranging from 100 to 800 units of any of the four vitamin D preparations are, on the whole, adequate to permit normal growth and to prevent the development of rickets in premature infants. The general health of all 166 infants carried through for eight months was excellent, and they had no clinical stigmas of rickets. Only 9 infants had any anatomic evidence of rickets as demonstrated on roentgenograms; at least 2 of these were doubtful. In none of these was an extension of the rachitic process in later films. Actually, several showed a restoration to normal without an increase in the dosage of vitamin D during the period of study.

The 23 instances of high phosphatase levels (and the 2 additional ones among the babies followed only for six months) without other chemical, roentgenographic or clinical evidence of rickets poses the important question of how significant is the finding of phosphatase levels above 15 units per hundred cubic centimeters. Our own feeling is that such an

isolated observation is not indicative of incipient rickets. It may represent a danger signal implying the imminence of rickets. But even this conclusion could not be documented from our data. Most of the infants with phosphatase levels above 15 units not only did not progress to rickets but actually showed lower phosphatase levels later in the study. The use of 20 units per hundred cubic centimeters as a dividing line between normal and possible rickets gives a much more reasonable distribution of the high phosphatase concentrations in keeping with the clinical roentgenographic findings. With this gage, the total number of infants with high phosphatase levels, including those with roentgenographic signs, was 12, of which 10 were among the 100 and 200 unit groups.

The consistent finding of high serum concentrations of calcium and phosphorus, even in the presence of elevated phosphatase levels and roentgenographic signs of rickets indicates that at least for premature infants these determinations cannot be used as a test for early rickets. Lowering of the serum calcium and phosphorus concentrations appears as a relatively late phenomenon, usually at a time when clinical evidence of rickets is already present, as was pointed out by Eliot and Park.[1] The large number of high levels seen in these studies was probably related to the high mineral content of the diet utilized.

It is significant that the infants in all 16 categories showed a remarkable similarity in pattern of growth, both in length and in weight. Though there was some inhibition of gain in weight during the first two months associated with the low caloric diet, this delay was made up for in later months and both length and weight increased steadily and regularly for the entire period of study. The average length gained per day during the eight months of study was of the same order as reported by Stearns, Jeans and Vandercar [5] in their study of normal infants who received 340 to 400 units of vitamin D from cod liver oil daily. If vitamin D was needed for the normal growth of the premature infants, a daily dose of 100 units was as adequate to support that growth as doses up to 800 units.

No statistical evidence of the superiority of one vitamin D preparation over the others was obtained. The smallest number of elevated phosphatase levels occurred in the viosterol groups, but these groups contained 2 infants with roentgenographic evidence of rickets at the dosage of 800 units. On the other hand, the A. R. P. I. vitamin D_2 group, which had the largest number of phosphatase levels above 15 units per hundred cubic centimeters, had no infant with positive roentgenographic signs and only 2 infants with suspicious findings on the roentgenogram. With 20 units of phosphatase per hundred cubic centimeters as the upper limit of normal, the distribution of elevated phosphatase levels became nearly equal in all four vitamin D groups, the

group receiving viosterol still having the least number. In terms of promotion or allowance of growth in length and weight, all four vitamin D preparations appeared equally good. There was no evidence in either the ability to promote growth or the ability to prevent rickets that the theoretically purer crystalline vitamin D_2 was superior to the noncrystallized forms of the vitamin, whether the latter were prepared by ultraviolet irradiation or by electron bombardment. Similarly, vitamin D_3 gave no evidence in this study of having any advantage over any of the forms of vitamin D_2. Our observations substantiate the general conclusion suggested by Eliot and Park [1] that in human nutrition the various types of vitamin D commercially available are unit for unit indistinguishable from each other.

From the data reported, it appears that the minimal requirements of vitamin D for the premature infant are lower than those estimated by previous investigators. Actually, most of the reported investigations made no effort to reach the minimal dose. For example, McQuarrie and associates [6] in reporting on the efficacy of A. R. P. I. vitamin D_2 in the prevention of rickets in premature infants observed that 540 units per day was satisfactory but did not use any lower dosages. Our observations indicate that 100 units per day will probably protect even the Negro premature infant from rickets. However, the greater incidence of elevated phosphatase levels in the 100 and 200 unit groups makes both these dosages too unsafe for recommendation. Even if these dosages are adequate they leave an insufficient margin of safety in case of illness or temporary neglect on the part of the mother. With the present availability of concentrates of vitamin D in comparatively cheap form there is no good reason why 400 or even 800 units per day should not be given as the prophylactic dose.

SUMMARY

The efficacy of four vitamin D preparations in preventing rickets and allowing normal growth was studied in 166 premature infants for the first eight months of their lives. The preparations were (1) vitamin D_2 (American Research Products, Inc. process), made by electron bombardment of ergosterol, (2) viosterol, which is vitamin D_2 made by ultraviolet irradiation of ergosterol, (3) crystalline vitamin D_2 and (4) "delsterol" (vitamin D_3), made by irradiation of 7-dehydrocholesterol. The dosages used were 100 units, 200 units, 400 units and 800 units daily.

No instances of clinical rickets were observed. Roentgenographic evidence of rickets occurred in 7 infants; in 2 others there was suspicious bowing of the extremities.

Phosphatase levels above 15 Bodansky units per hundred cubic centimeters occurred in 29 instances, of which 23 were unaccompanied

by any evidence of rickets. It is believed that 20 units per hundred cubic centimeters represents a better normal upper limit for premature infants. With this limit, 12 instances of elevated phosphatase levels occurred, 10 of which were in the groups receiving 100 and 200 units.

Serum calcium and phosphorus concentrations were almost always at high normal levels, even in the presence of roentgenographic evidence of rickets.

Gain in weight and length was uniformly good in all 166 infants, regardless of the dosage or the type of vitamin D used.

There appeared to be no difference in the efficacy of the vitamin D preparations in preventing rickets or in allowing growth; the crystalline vitamin D_2 was no better than the noncrystalline forms, and vitamin D_3 showed no superiority over any of the vitamin D_2 preparations used.

Though 100 units of vitamin D is a satisfactory prophylactic dose for most premature infants, 400 or 800 units daily allow a greater margin of safety in cases of illness or temporary neglect.

629 South Wood Street (12).

WHOOPING COUGH TREATED WITH PERTUSSIS IMMUNE SERUM (HUMAN)

Report on a Controlled Series of Fifty-Two Patients Under One Year of Age

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THE TREATMENT of whooping cough is a problem which still presents a challenge. Its high mortality and severity in the younger age group have focused attention of physicians on this disease in an effort to find better ways to treat it. Until about ten years ago, the treatment of whooping cough was entirely symptomatic, but at present, with the use of convalescent serum and immune whole blood, the employment of potent or high titer serums is encouraged. These serums are obtained from human beings, or from rabbits, who have been repeatedly immunized with pertussis vaccine.

Bradford,[1] in 1935, using immune blood from patients, concluded that it was probably effective in the prevention and modification of whooping cough if given before the catarrhal symptoms appear. The benefit was less apparent when given after the disease was established.

Using the opsonocytophagic index and the decrease in the number of lymphocytes as indications of therapeutic response, Katsampes and associates[2] in 1939 reported that therapeutic effect was absent in 1 patient, doubtful in 1, marked in 4 and definitely present in 12 patients under 1 year of age who were treated in the early stage of the disease with 20 to 40 cc. of pertussis immune serum (human) N. N. R. given intramuscularly.

McGuinness and associates[3] in 1940 reported that hyperimmune human whooping cough serum gave "excellent" results in 32 patients, "good" results in 31 and "moderate" improvement in 20. The benefit was "questionable" in 14, and 3 patients died. These patients were given from two to four doses of from 10 to 20 cc. each. The 3 deaths

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From the Philadelphia Hospital for Contagious Diseases.

1. Bradford, W. L.: Use of Convalescent Blood in Whooping Cough, with Review of Literature, Am. J. Dis. Child. **50**:918-928 (Oct.) 1935.

2. Katsampes, C.; McGuinness, A. C., and Bradford, W. L.: Effect of Hyperimmune Human Serum (Lyophile) on the Humoral Antibody Titer in Pertussis, Am. J. Dis. Child. **58**:1234-1239 (Dec.) 1939.

3. McGuinness, A. C.; Bradford, W. L., and Armstrong, J. G.: Production and Use of Hyperimmune Human Whooping Cough Serum, J. Pediat. **16**:21-29, 1940.

occurred in infants 2 months of age, representing a mortality rate of 5.9 per cent in the group of patients under 6 months of age. In the authors' opinion the infants responded to the serum better than did older patients.

In 1944, McGuinness and others [4] reported their results in a series of 442 patients (which included 100 patients reported on in 1940 [3]). Of 236 infants under 1 year of age, "good" and "excellent" results were obtained in 168 (71.1 per cent) and "moderate" to "poor" results in 63 (26.7 per cent). There were 5 deaths (2.1 per cent) in this group. All deaths occurred in infants under 6 months of age who had pneumonia, but none received the recommended minimum dose of serum before death. The dose of serum used in this series was 20 cc. given intramuscularly at forty-eight hour intervals for three doses. It is not stated in the report at what stage of the disease the specific therapy was instituted, nor were control cases used.

Cohen and associates,[5] Scheinblum and his co-worker [6] and Felton [7] claimed beneficial effects with hyperimmune serum in treatment of pertussis. Lapin [8] used a globulin fraction of human hyperimmune serum, giving four doses of 2.5 cc. each. Except for 2, all his patients were over 1 year of age. Of the 2 under 1 year of age, one 0.3 year old on the seventh day of cough was reported as being "markedly" improved, with no whoop but with a cough for four weeks. The other, 0.4 year of age, showed "no improvement" but had whoop and emesis and coughed for five weeks. Lapin reported 28 per cent "failure" among his patients in this study. None of the authors used controls in their investigations.

Kohn and associates [9] recently reported on a series of 152 patients who received hyperimmune antipertussis human serum. Of the 79 infants under 1 year of age, they reported "improvement" in 70, no "change" in 8 and 1 death (1.2 per cent). There were no controls and results were classified according to impression of the attending staff. Serum was given intramuscularly and in doses equal to 20 cc. of serum for three doses.

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4. McGuinness, A. C.; Armstrong, J. G., and Felton, H. M.: Hyperimmune Whooping Cough Serum: Further Studies, J. Pediat. **24**:249-258 (March) 1944.

5. Cohen, P.; Weichsel, M., and Lapin, J. H.: Comparative Study of Therapeutic Agents in Treatment of Pertussis, J. Pediat. **16**:30-35 (Jan.) 1940.

6. Scheinblum, I. E., and Bullowa, J. G. M.: Treatment of Pertussis with Lyophile Hyperimmune Human Pertussis Serum, J. Pediat. **25**:49-55 (July) 1944.

7. Felton, H. M.: Status of Passive Immunization and Treatment in Pertussis by Use of Human Hyperimmune Serum, J.A.M.A. **128**:26-28 (May 5) 1945.

8. Lapin, J. H.: Serum in Prophylaxis of Contacts and Treatment of Whooping Cough, J. Pediat. **26**:555-559 (June) 1945.

9. Kohn, J. L.; Rudel, G. H.; Weichsel, M., and Buxbaum, L.: Hyperimmune Serums in Treatment of Whooping Cough, Am. J. Dis. Child. **74**:321-333 (Sept.) 1947.

It is generally recognized that the disease is severest and is attended with the highest mortality rate in patients under 1 year of age. For this reason, only patients in this age group were admitted to our study. The period of observation extended from February 1944 to May 1945.

MATERIAL AND METHOD

All patients with whooping cough up to and including 12 months of age were admitted to the study. Only those patients for whom the diagnosis of whooping cough was confirmed by laboratory studies and by clinical evidence were kept in the series. Patients were divided into two groups; each group included the alternate patients admitted without selection.

Except for pertussis immune serum (human), the patients in group 1 were treated as those in group 2. Each patient of group 2, the control group, was treated in the usual manner, which consisted of sedation, aspiration, and administration of sulfonamide drugs and/or penicillin for bacterial complications, oxygen and a mixture of 5 per cent carbon dioxide and 95 per cent oxygen. Blood transfusions were withheld whenever possible.

Serum.—The serum used in this study was prepared in the usual manner; it had an agglutinin titer of 1:2,560 or higher and was supplied from a single

TABLE 1.—*Frequency of Dose of Pertussis Immune Serum (Human) for 26 Patients*

Doses	2	3	4	5	6	Total
Number of Patients	3	11	5	3	4	26

lot. This serum was prepared by pooling the bloods of a number of healthy adults who had had whooping cough in childhood and whose protective substances had been fortified by repeated courses of phase I pertussis vaccine.

With the exception of a few doses, all serum was administered intravenously. On admission to the hospital, 50 to 100 cc. of serum was given, depending on the condition of the patient, and this was followed by a daily injection of 50 cc. until there was clinical improvement or until five doses were given. The last 9 patients in group 1 were given the serum every other day in order to determine whether the response would be improved by extending the treatment over a longer time. When large volumes of fluid intravenously were considered inadvisable, the vacuum-dried serum was restored to 25 or 50 per cent of its full dilution.

Laboratory Studies.—Cultures: The method described by Brooks, Bradford and Berry[10] was employed. A cotton-tipped nichrome wire applicator was inserted via the nose to the pharynx and held in place for one minute or until the patient coughed. Penicillin-treated Bordet-Gengou plates were inoculated with the nasopharyngeal swab and examined by the City Laboratory of Philadelphia. Simultaneously, a second nasopharyngeal swab was used to inoculate a broth culture medium, which was examined by Dr. A. Bondi, of the Department of Bacteriology, Temple University Medical School. At least two sets of cultures were taken of each patient, the first one on admission and the second on the following morning.

10. Brooks, A. M.; Bradford, W. L., and Berry, G. P.: The Method of Nasopharyngeal Cultures in the Diagnosis of Whooping Cough, J. A. M. A. **120**: 883-885 (Nov. 21) 1942.

Complete blood counts were made on admission and as often as indicated. Roentgenograms of the lungs were taken of patients with suspected pneumonia.

The number of paroxysms and the frequency of emesis and cyanosis were recorded by the nurses on charts kept at the cribside. Graduate nurses who were experienced in the care of patients with whooping cough were always in charge of the ward. The clinical picture of the patient, as reflected by the number of paroxysms, frequency of emesis, temperature changes, number of aspirations and the general appearance, was to be used to study the course of the disease.

RESULTS

There were 52 patients in this study, 26 of whom were in the serum group. The day of disease was counted from the first day of cough, as obtained from the history. The patients were well distributed by age, sex and race, as noted in table 2.

A review of the records kept at the cribside demonstrated that emesis was related directly to the severity and frequency of attacks of

TABLE 2.—*Distribution of 52 Patients Under 1 Year of Age, with Whooping Cough, According to Age and According to Race and Sex*

Age, Mo.	0 to 3	4 to 6	7 to 9	10 to 12	Total
Serum group	9	7	5	5	26
Control group	6	9	5	6	26

	Race				
	Negro		White		
Sex	Girls	Boys	Girls	Boys	Total
Serum group	10	7	5	4	26
Control group	8	11	4	3	26

paroxysms. Cyanosis depended on the duration of paroxysms of coughing rather than on their severity. A decrease in the frequency of the paroxysms of cough was considered a sign of improvement. The effect on the frequency of the cough was compared in the two groups. The groups were subdivided according to the week of disease when treatment was instituted.

The curve of the mean was employed by Kerley,[11] Miller and Singer-Brooks [12] and others to study the course of the whooping cough. Because of the wide range in the number of daily paroxysms in several of our patients, the mean was greatly affected by 1 or 2 patients with a high frequency of paroxysms. The introduction of a new patient to the series with either an extremely low or an extremely high frequency

11. Kerley, C. G.: Treatment of Diseases of Children, Philadelphia, W. B. Saunders Company, 1907, p. 321.

12. Miller, J. J., Jr., and Singer-Brooks, C.: Variable Course of Pertussis: Does Haemophilus Pertussis Undenatured Bacterial Antigen Alter It? Am. J. Dis. Child. **53**:720-738 (March) 1937.

of paroxysms also caused an abnormal change in the smoothness of the curve. In order to overcome this erroneous impression, the sum of the daily frequency of paroxysms for the seven day periods of each patient was taken as the unit, and sums of the daily frequencies of paroxysms of the subsequent seven day periods were compared with it. By this method, the relative number of paroxysms for each patient is obtained. To demonstrate graphically the rate of change in the frequency of paroxysms for each group, a semilogarithmic chart is employed. There were only 2 patients in whom the duration of paroxysms was not longer than seven days and both of these were in the control group.

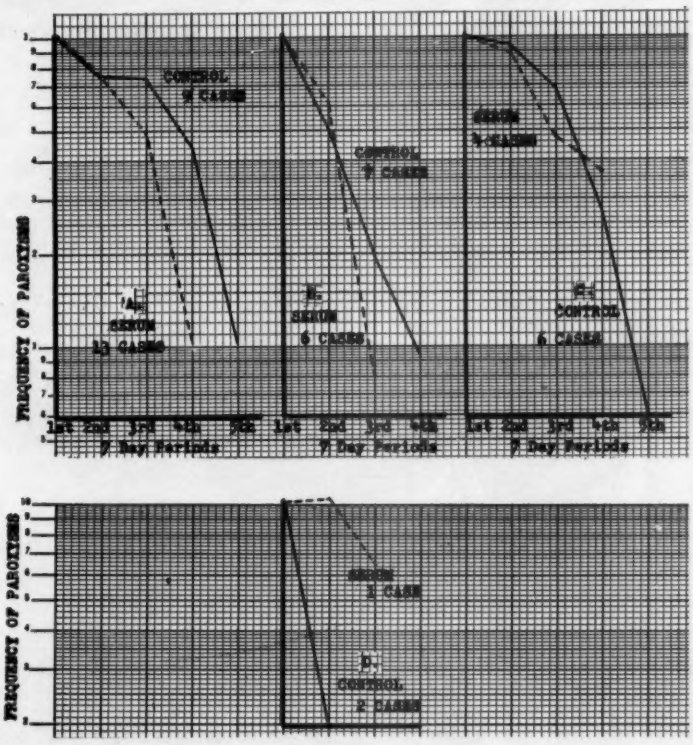

Chart 1.—Semilogarithmic chart showing rate of change in frequency of paroxysms for: *A*, cases in which treatment was started in the first week of whooping cough; *B*, those in which treatment was started in the second week; *C*, those in which treatment was started in the third week, and *D*, those in which treatment was started in the fourth week of whooping cough.

The patients who received serum in the first week of whooping cough showed a regular decrease in the rate of paroxysms over a four week period. The control patients in this group showed an identical decrease for the first two seven day periods, after which the rate of decrease in frequency of paroxysms lagged by seven days (part *A* of chart 1).

When treatment was started in the second week of whooping cough (part *B* of chart 1), the effect was similar to that observed when treatment was given in the first week, in that both groups showed a comparable decrease in paroxysms for the first two seven day periods, after which the rate of decline for the serum group was more rapid.

The decrease in frequency of paroxysms in the patients who were treated in the third week of disease (part *C* of chart 1) showed no notable difference in the two groups. The number of patients treated in the fourth week of whooping cough is too small to warrant comment.

In order to determine the influence of serum on whooping cough complicated by bronchopneumonia, this group of patients was analyzed

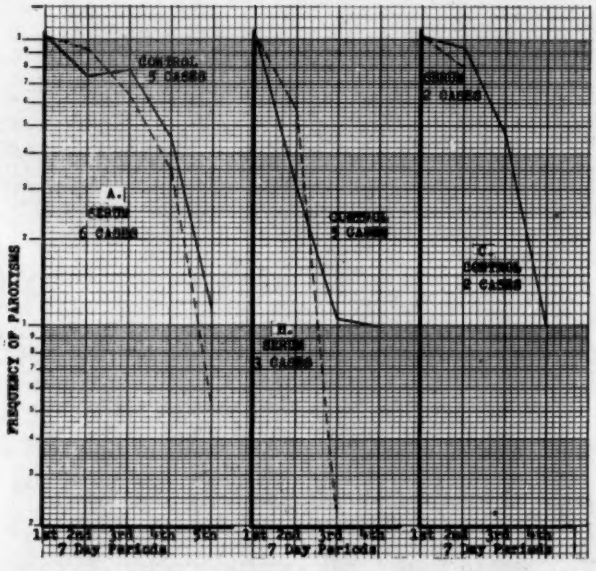

Chart 2.—Semilogarithmic chart showing rate of change in frequency of paroxysms in cases of whooping cough with bronchopneumonia. *A* shows curves for cases in which treatment was started in the first week of illness; *B* for cases in which treatment was started in the second week of illness, and *C*, for cases in which treatment was started in the third week of illness.

separately. There were 26 patients with bronchopneumonia in the entire series of 52 patients (the records of the number of paroxysms of 3 patients were inadequate to include in the chart). The diagnosis of pneumonia was made by physical examination or by roentgenogram, or both. Eleven patients with pertussis and bronchopneumonia received hyperimmune serum.

The rate of decrease in frequency of paroxysms in patients with whooping cough and pneumonia treated in the first week of disease was slightly better in the serum group but less pronounced than shown in chart 1.

All the patients with pneumonia treated in the first week of pertussis coughed more frequently but not longer than the patients without pneumonia. This was more noticeable in the group of patients receiving serum than in the control group. There was no great difference in the rate of decline in the frequency of paroxysms between the control and the test patients in the group with pneumonia.

CULTURES

There were only 3 patients whose nasopharyngeal cultures were reported as yielding Hemophilus pertussis. Two of these positive cultures were obtained from control patients with pneumonia, one admitted on the second day of disease, the other on the tenth day of disease. The third positive culture was obtained from a patient treated with serum who was admitted on the fifth day of disease. This represents 13.1 per cent of cultures yielding the organism in the patients examined in the first week of disease.

TABLE 3.—*Duration of Fever in Days of 52 Patients Under 1 Year of Age with Whooping Cough*

	Serum Group		Control Group	
Week of Disease	Fever Without Pneumonia, Duration, Days	Fever with Pneumonia, Duration, Days	Fever Without Pneumonia, Duration, Days	Fever with Pneumonia, Duration, Days
First	5.2	8.3	3.0	2.7
Second	4.8	4.8	3.4	3.4
Third	17.7	17.6	5.3	11.0

FEVER

The duration of fever in either group was not strongly influenced by the presence of pneumonia. In general, the patients who were admitted late in the course of the disease were sicker and had a protracted fever. For this study, all temperatures of 100 F. (rectal) and higher were considered significant.

LYMPHOCYTOSIS

Nearly all the patients had leukocytosis and all the blood counts showed lymphocytosis. Approximately two thirds of the patients with leukocytosis of more than 20,000 cells had bronchopneumonia. In these patients, the relative lymphocytosis was not greater than in the non-pneumonia patients with a leukocyte count of more than 20,000 cells nor was it greater in those with a leukocyte count of less than 20,000. The relative lymphocytosis was highest in the first week of disease, ranging from 59 to 96 per cent, and remained high even in the third week, ranging from 39 to 81 per cent. The highest white blood cell count in this study was 70,200, which was found in a patient with

pneumonia in the third week of whooping cough. There was only 1 patient with a white blood cell count of less than 10,000 in the first week of disease, and this patient had a differential count of 72 per cent lymphocytes.

COMPLICATIONS

Ordinarily only patients with whooping cough and complications are admitted to the hospital. However, because of social or economic reasons, patients without complications, particularly those under 1 year of age, are admitted for treatment.

Pneumonia was the most frequent complication in this group, being diagnosed in 26 (50 per cent) of our patients; 13 were in the control group and 13 in the serum group. Otitis media was present in 11 (21 per cent), diarrhea in 9 (17 per cent), convulsions in 3 (6 per cent) and encephalitis in 1 (2 per cent).

TREATMENT

In addition to specific serum in the test group, treatment comprised sulfonamide drugs for bacterial complications in 16 control cases and in 12 of the serum (test) group, a mixture of 5 per cent carbon dioxide and 95 per cent oxygen by inhalation for cyanosis during a paroxysm, use of an oxygen tent for continued cyanosis and blood transfusions for correction of anemia and for supportive treatment. Blood transfusions were given to 7 patients, 5 of whom were in the control group. Except for case 1, described later, all patients who received blood transfusions had pneumonia.

Characteristics of the severe cases are illustrated by the following 3 case reports:

CASE 1.—W. W., a 5 month old Negro boy, was admitted on the nineteenth day of whooping cough with convulsions and apnea. He had been in coma since the day before hospitalization. This patient was given sulfadiazine, oxygen inhalations, sedation and one transfusion of 100 cc. of fresh citrated blood. Except for several attacks of apnea, which responded to symptomatic treatment, the course was uneventful and he was discharged as recovered after six weeks in the hospital.

CASE 2.—D. H., a 5 month old white girl, was admitted on the fifth day of whooping cough with convulsions and diffuse bronchopneumonia, the presence of which was confirmed by roentgenographic examination. The spinal fluid showed 480 cells with 76 per cent lymphocytes. Four days later the spinal fluid showed 18 cells with 60 per cent lymphocytes. The fever ranged between 101 and 104 F. for the first eight days in the hospital. She was treated with daily intravenous injections of hyperimmune serum over a five day period, receiving a total of 390 cc. On the fourth day, the first of several blood transfusions, which totaled 285 cc., was given. Other treatment included oxygen, sedation and sulfonamide therapy. This patient never had frequent or severe paroxysms. She coughed from 2 to 10 times daily for the first ten days, thereafter from 2 to 4 times daily.

CASE 3.—W. H., a 10 month old Negro boy, with whooping cough and primary pulmonary tuberculosis of three months' duration, who was treated in the control

group recovered from the whooping cough but died of miliary tuberculosis three months later. This was 1 of the 3 patients who had a cough plate which yielded H. pertussis.

There was only 1 death from whooping cough in this study. An 8 month old Negro girl with pertussis and bronchopneumonia in the serum group was admitted to the hospital on the fourteenth day of disease. In spite of 180 cc. of hyperimmune serum, sulfonamide drugs and penicillin, she grew progressively worse and died eleven days after admission, on the twenty-fifth day of disease. Autopsy showed atelectasis of the lungs, emphysema and purulent bronchopneumonia.

COMMENT

It is difficult to evaluate the effect of any agent on a disease which is as unpredictable and variable as whooping cough. The severity and mortality in this disease vary widely from year to year and from patient to patient. The variable factors, such as difference in age, difference in seasons, sex, race, previous state of nutrition and complicating diseases, must be either eliminated or controlled in order to determine the influence of therapeutic agents on the disease. By taking the patients alternately over a continuous period of fifteen months until 52 cases were observed, we were able to have an even distribution by age, sex, race, severity of disease and incidence of pneumonia. It is not proper to rely accurately on a comparison of the disease from year to year when evaluating treatment. The frequency of paroxysms was used as an index for following the course of the disease. According to Kerley,[11] Miller and Singer-Brooks [12] and Bamberger and Menke,[13] who used the average of the daily frequency of paroxysms, it was observed that in untreated patients the peak of frequency was reached between the eighth and twelfth day of whooping. If a therapeutic agent is used before this time, its effect cannot be judged because the disease may have been mild anyway. The study undertaken by us merely compares two comparable groups of patients, and any difference in the course of the disease may be attributed to the hyperimmune serum. The method of charting the course of whooping cough by using the average of the daily paroxysms described by others cannot be applied to a small number of patients. If the number of paroxysms for a given period for each patient is taken as a unit, then the sum of the paroxysms of similar subsequent periods can be given relative values. Except for a slightly better response in the group treated with serum when treatment was started in the first week of disease, the influence on the frequency of paroxysms and on the rate of decline in the frequency was not striking. This response could probably be attributed to the effect of serum on the patients without complications as it was not observed in the patients with pneumonia.

13. Bamberger, P., and Menke, H.: Der Normalverlauf der Keuchhustenerkrankung als Maszstab zur Beurteilung von Heilversuchen, Klin. Wchnschr. 14:1036-1039 (July 20) 1935.

An analysis of the duration of the disease, based on the assumption that when the number of paroxysms exceeds 2 daily the disease was still active, showed that the group of patients with uncomplicated whooping cough treated with serum in the first week of disease was the only group which approached the borderline of statistical significance (standard error 1.7).

There was no dramatic change in the disease in our patients who received serum. The temperature remained elevated longer in patients in the serum group than it did in the control group. Several factors as to the cause of the fever are to be considered. Pneumonia was usually responsible for fever, although other bacterial complications, particularly otitis media and purulent rhinitis, have to be considered. These complications were nearly equally divided between the two groups in our study. Although there was no evidence of untoward reaction to the serum, the possibility of a febrile reaction from this cause must be kept in mind.

The difference in mortality rate is not significant.

Only 9 patients received serum on alternate days, and the effect on these patients was no different from that obtained with daily doses. The conclusions of this study are not to be considered as final since the groups are undoubtedly small. When the groups are subdivided they become almost insignificant. It is recommended that before any therapeutic agent for whooping cough is considered effective it should be tried on a large number of patients in well controlled series.

SUMMARY AND CONCLUSIONS

Fifty-two patients under 1 year of age with whooping cough were studied to determine the effect of large doses of pertussis immune serum (human) N. N. R. in alternate patients. The patients were well distributed by age, sex, race, complications and treatment. The patients who received serum showed a more regular decline in the rate of frequency of paroxysms when treated in the first week of disease than did the patients in the control group. The difference was not as noticeable when treatment was started in the second week of disease. In both instances, the difference was not apparent until after the second seven day period after hyperimmune serum was given.

The serum did not materially affect the rate of decline of the frequency of paroxysms in patients with bronchopneumonia as compared with controls. The temperature remained elevated longer in patients treated with serum than in the control patients.

4000 North Front Street (40).

MEASLES ENCEPHALITIS

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INTEREST in encephalitis associated with measles has increased considerably within the last two decades. At the time of an earlier report by Neal and one of us (E. A.)[1] in 1927, this condition was just beginning to be generally recognized as a distinct clinical entity. In 1928, Ford,[2] in an excellent paper, collected 113 cases from the literature and added 12 of his own. Subsequent detailed clinical records were given by Peterman and Fox[3] in 1939, by Hamilton and Hanna[4] in 1941 and by Litvak and associates[5] in 1943. Reports dealing with the pathologic aspects of this condition by Wohlwill[6] appeared in 1928, by Zimmerman and Yannet[7] in 1930, by Ferraro and Scheffer[8] in 1931,

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From the Willard Parker Hospital and from the Bureau of Laboratories, New York City Department of Health.

1. Neal, J. B., and Appelbaum, E.: Encephalitis Associated with Measles, J.A.M.A. **88**:1522 (May 14) 1927.

2. Ford, F. R.: The Nervous Complications of Measles, with Summary of Literature and Publication of Twelve Additional Case Reports, Bull. Johns Hopkins Hosp. **43**:140 (Sept.) 1928.

3. Peterman, M. G., and Fox, M. J.: Postmeasles Encephalitis, Am. J. Dis. Child. **57**:1253 (June) 1939.

4. Hamilton, P. M., and Hanna, R. J.: Encephalitis Complicating Measles: Report on Two Hundred and Forty-One Cases from the Literature and on Forty-Four Additional Cases, Am. J. Dis. Child. **61**:483 (March) 1941.

5. Litvak, A. M.; Sands, I. J., and Gibel, H.: Encephalitis Complicating Measles: Report of Fifty-Six Cases with Follow-Up Studies in Thirty-Two, Am. J. Dis. Child. **65**:265 (Feb.) 1943.

6. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

7. Zimmerman, H. M., and Yannet, H.: Encephalomyelitis Complicating Measles: Report of Case with Necropsy, Arch. Neurol. & Psychiat. **24**:1000 (Nov.) 1930.

8. Ferraro, A., and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles, Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748 (April) 1931.

by Finley[9] in 1937, by Malamud in 1937[10] and in 1939[11] and by Ziskind and Schattenburg[12] in 1939.

Our own extensive clinical material on measles encephalitis with follow-up observations on a large number of cases and with pathologic study of several others prompted this report. In view of the amazing progress recently made in the control of measles as regards its prevention or modification by the use of human gamma globulin, the continued unabated occurrence of the dreaded complication of encephalitis presents a challenge to the medical profession. Since the disease process may involve the spinal cord, as well as the brain, this entity would perhaps better be called measles encephalomyelitis. We shall, however, adhere to the more commonly employed term measles encephalitis, particularly since cases showing clinical evidence of involvement of the cord are not common.

MATERIAL

The material in the present study consisted of 74 cases with involvement of the central nervous system—encephalitis, myelitis, or both—in association with an attack of measles, which were observed by us at the Willard Parker Hospital from May 1936 to June 1946. The material included necropsy studies on 6 patients and follow-up studies on 33.

ETIOLOGIC ASPECTS

The etiology of measles encephalitis is unknown. The most commonly held views are: (1) the theory that the disease is actually due to the virus of measles; (2) the activation theory, that the measles virus activates another virus which is dormant in the patient, and (3) the allergic theory, that the condition is due to an allergic response of the central nervous system to the virus of measles.

The first view, which regards the measles virus as the cause, received recent impetus from the work of Shaffer, Rake and Hodes.[13] These workers reported that they recovered the measles virus from the brain of a child who died of measles encephalitis nine days after the appearance of the rash. They were able to produce signs characteristic of measles in 2 monkeys which they inoculated with a brain suspension

9. Finley, K. H.: Perivenous Changes in Acute Encephalitis Associated with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **37**:505 (March) 1937.

10. Malamud, N.: Encephalomyelitis Complicating Measles, Arch. Neurol. & Psychiat. **38**:1025 (Nov.) 1937.

11. Malamud, N.: Sequelae of Postmeasles Encephalitis: Clinicopathologic Study, Arch. Neurol. & Psychiat. **41**:943 (May) 1939.

12. Ziskind, J., and Schattenburg, H. J.: Postmeasles Encephalitis, Arch. Path. **27**:128 (Jan.) 1939.

13. Shaffer, M. F.; Rake, G., and Hodes, H. L.: Isolation of Virus from Patient with Fatal Encephalitis Complicating Measles, Am. J. Dis. Child. **64**:815 (Nov.) 1942.

from this patient. The second view mentioned, which regards measles encephalitis as being due to the activation of a latent virus by the measles virus, was supported by Greenfield.[14] He noted the clinical and pathologic similarity of the encephalitis following measles, vaccination and smallpox and argued that the virus of these diseases stimulates a latent virus to activity. The third theory ascribes measles encephalitis to an allergic response of the brain. This view was staunchly supported by Finley.[15] Using Ford's [2] collected cases of measles encephalitis, he held that the incubation period of measles encephalitis in relation to the appearance of the exanthem is fairly constant and that this argues in favor of an allergic causation of the nature of an antigen-antibody reaction.

PATHOLOGIC CHANGES

This section of the paper is based on the necropsy material from 7 cases. Six cases of measles encephalitis of less than one week's duration,

TABLE 1.—*Histologic Changes in 7 Cases of Measles Encephalitis*

Case Number	Duration of Neurologic Manifestation	Infiltration of Veins	Demyelination	Perivascular Hemorrhage	Cellular Changes	Meningeal Infiltration
Case 70	None	+	0	0	S* +	+
Case 1	1 day	++	0	0	A++	++
Case 57	3 days	++	0	0	A+++	0
Case 17	3 days	++	+	++	A++	++
Case 37	3 days	++	+++	0	A+	0
Case 45	6 days	+	+++	0	S +	0
Case 75	11 days	+	+++	0	A++ S + (Spinal cord)	+ (Spinal cord)

* S indicates presence of "severe cellular damage" of Nissl and A, anoxemic changes.

belonging to the series of 74 cases analyzed here, presented a pathologic picture which differed considerably from the classic description of the changes in that cerebral complication of measles. The seventh case, which came to necropsy subsequent to the ten year period covered in this review, was included because, as the case of longer clinical duration, it presented the accepted features of measles encephalitis and, thus, helped to give a complete picture of the various pathologic changes occurring in that condition. Clinical evidence of encephalitis of from one to eleven days' duration was present in 6 cases, and in 1 case no neurologic manifestation was noted, but encephalitis was observed on routine examination of the brain of an infant who died of measles (case 1).

14. Greenfield, J. G.: The Pathology of Measles Encephalomyelitis, Brain **52**:171 (July) 1929.

15. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047 (May) 1938.

The histologic changes in the 7 cases are summarized in table 1.

The histologic picture of measles encephalitis which is generally known is that of perivascular loss of myelin (fig. 1). However, as seen from the table, this lesion was observed in only 4 of 7 cases; namely, in those in which clinical encephalitis had been presented for three days or longer. There was no demyelination in the case without clinical

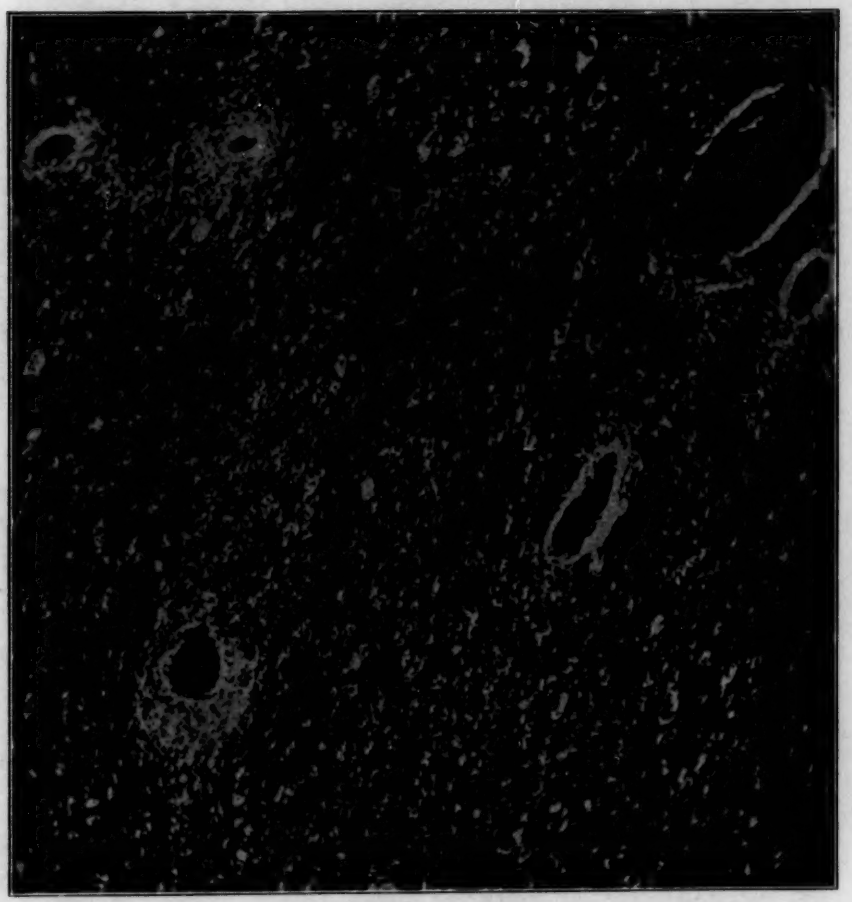

Fig. 1 (case 17).—Perivascular demyelinization in encephalitis of three days' duration.

manifestations of cerebral complications, in the case of one day's duration (fig. 2) and in 1 of the cases with a three days' history.

Vascular Changes.—One feature, however, was common to all cases and was most pronounced in those with a short history of neurologic manifestations. This feature was cellular infiltration of the walls of small and medium-sized veins in the gray and white matter of the brain (fig. 3). In the case without clinical evidence of encephalitis these

lesions were seen mainly in the gray nuclei of the pons, but not in the white matter. The cases of one and three days' duration showed the widest distribution of these lesions, independent of the presence or absence of demyelination. In the cortex, the vascular lesions were observed in all layers of Brodmann, even in the first, especially in the cases with meningeal infiltration; numerous veins with infiltrated walls were also present in the cortical white matter and in the internal capsule. Other

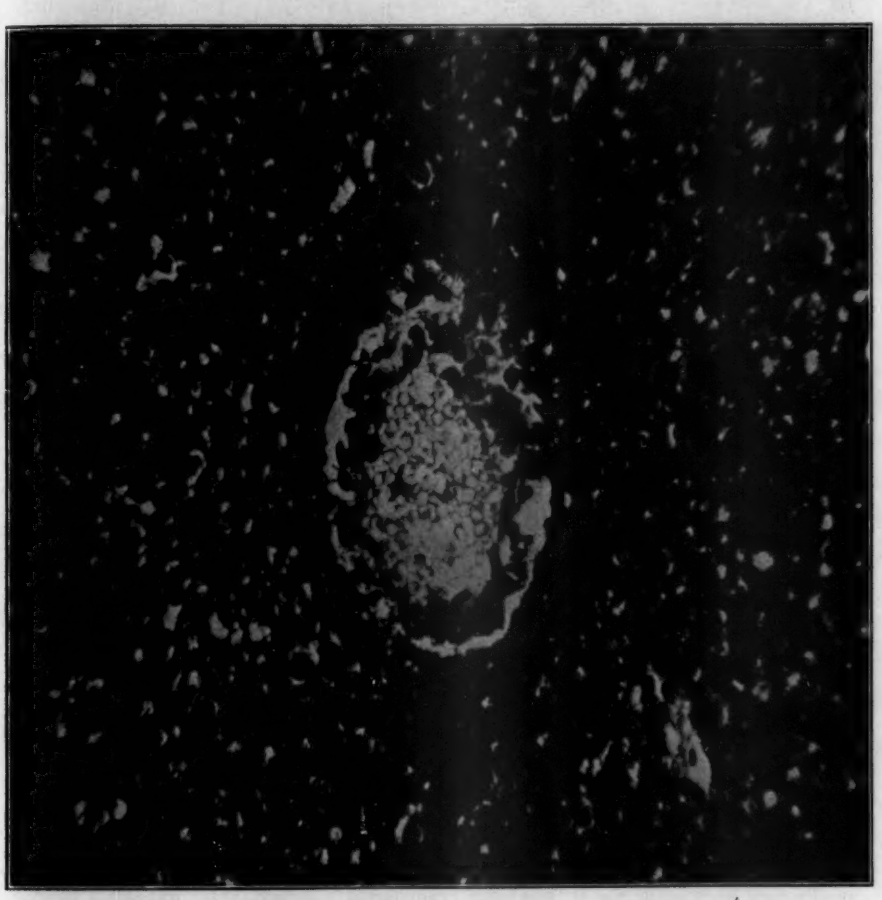

Fig. 2 (case 1).—Mononuclear infiltration of the wall of a vein in the white matter, with no demyelination in encephalitis of one day's duration.

gray areas involved were the hippocampus, the basal ganglions and the gray nuclei of the pons. In the cerebellum the lesions were seen in the central white matter of the dentate nucleus, and occasionally outside the structure. In the case of six days' duration slight infiltration of the vascular walls was seen in the cortex only, and in the case of eleven days' duration a few veins in the basal ganglions and in the gray matter of the pons were affected. The infiltrating cells were predominantly lympho-

cytes, but in some of the early cases a few polymorphonuclear cells were encountered. They were located in the adventitia of the veins and were arranged in one or two rows completely encircling the blood vessel. In the later cases microglial phagocytes were also present and were especially numerous in the case of eleven days' duration. In that case, the affected veins were in the vicinity of small areas of softening of the white matter.

Cellular infiltration of the vascular walls is only rarely mentioned in the literature on measles encephalitis. Finley [9] apparently was the first to call attention to the constancy and widespread distribution of

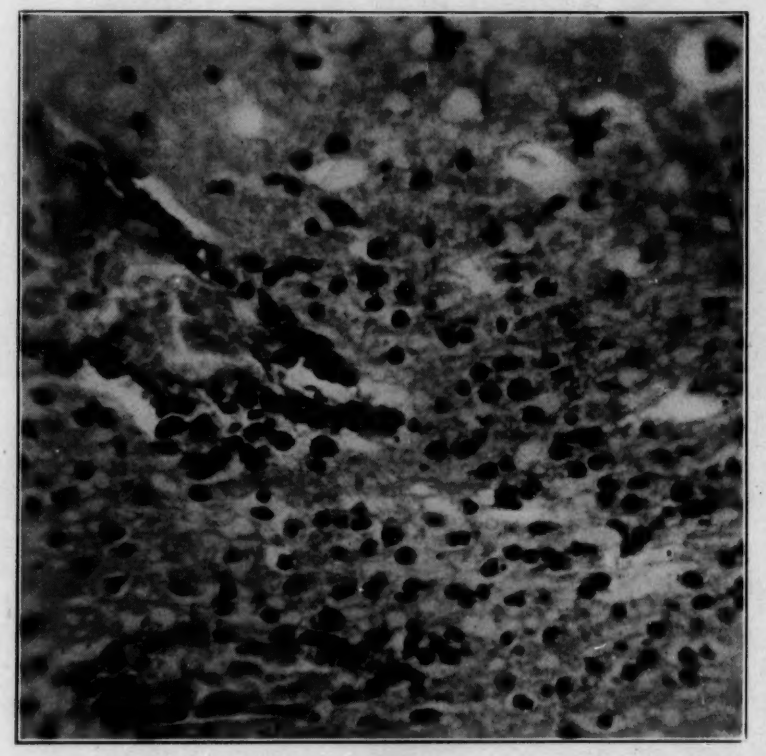

Fig. 3 (case 1).—Mononuclear infiltration of veins at the junction of the gray and white matter in encephalitis of one day's duration. Loose collections of glial nuclei may be seen in the surrounding brain tissue. Hematoxylin and eosin stain.

the infiltration of vascular walls in the gray matter of the brain in encephalitides complicating smallpox vaccination, smallpox and measles.

Demyelination.—Demyelination observed in 4 of our cases presented the usual perivascular distribution occurring in measles encephalitis. The destruction was severest in the case of eleven days' duration, in which the foci were large and often contiguous. There also were small areas of softening in the white matter not immediately adjacent to blood vessels. The demyelinated areas were infiltrated with microglial cells which even

in the cases with three days' history were often devoid of processes. Neutral fat was present in those cells only in the case of eleven days' duration, in which they became converted into frank gitter cells. In 1 case of this series, the case which showed widespread perivascular hemorrhages, some red cells and a few polymorphonuclear cells were also present in the demyelinated areas.

Thrombi.—Venous thrombi were not a constant or important observation in our material. In 2 cases, loose fibrinous thrombi were present in

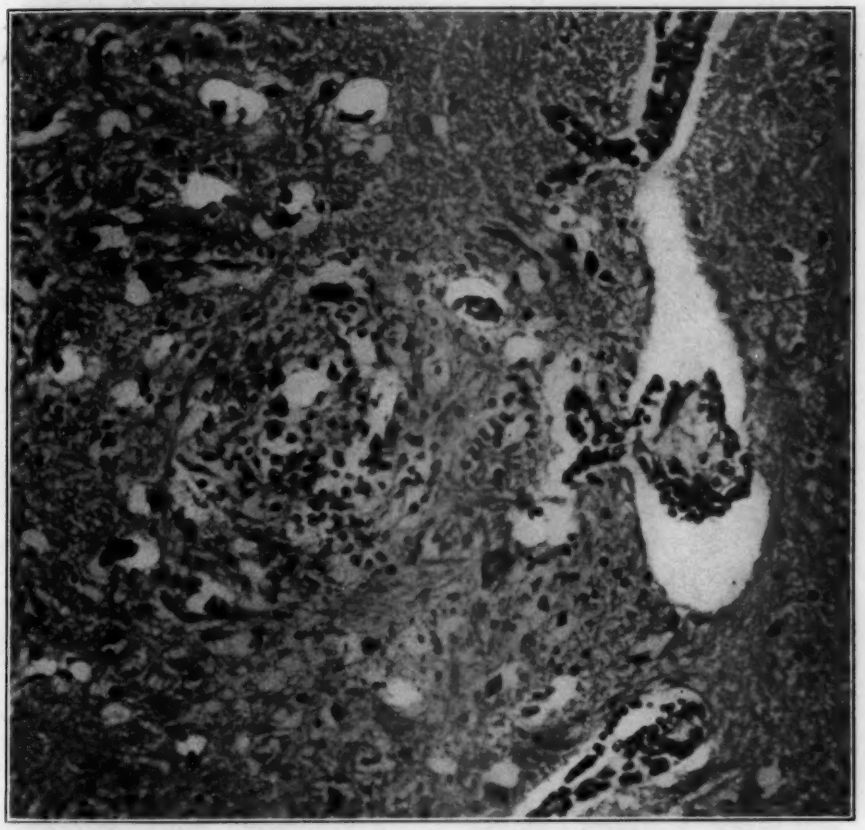

Fig. 4 (case 1).—"Cellular incrustations" (a form of anoxemic degeneration) in the temporal cortex in encephalitis of one day's duration. Cresyl violet stain, × 880.

a few veins within the demyelinated areas, but the majority of veins in such areas were free of thrombi. Occasional loose strands of fibrin were seen in veins not related to any perivascular lesions, usually in patients with terminal pneumonia. In 1 case, in sections stained for myelin, the lumens of several veins contained diffusely distributed black material resembling hyaline thrombi; however, in hematoxylin and eosin preparations one could clearly see the outlines of partly hemolyzed, but not fused, red cells in the lumens of those vessels.

Cellular Degeneration.—Significant changes in ganglion cells were observed in all cases. In 3 cases the focal "severe cellular damage" of Nissl was present, with neuronophagia in 2 of them. In 1 case, the damaged cells were located in the nuclei of the sixth and seventh nerves, and in the second, in both nuclei of the fifth nerve (fig. 4). In the third case, that of eleven days' duration, many ganglion cells of the anterior horns in the sacral portion of the cord were missing and a few cells in the lumbar portion were damaged; despite considerable diffuse proliferation of microglia in those areas there were no "microglial nodules." "Eosinophilic" or "homogenizing" anoxemic changes of cellular cytoplasm [16]

Fig. 5 (case 70).—"Severe cellular degeneration" in the nucleus of the fifth nerve, with neuronophagia (glial nodule) and mononuclear infiltration of the vascular wall. Clinical evidence of encephalitis was not present. Hematoxylin and eosin stain.

were present in 5 cases, and, in 1 of them, in addition, "cellular incrustations" were observed (fig. 5), which are also attributed to anoxemia.[17]

Gliosis.—Microglial response to the damage of myelin was discussed in the paragraph on demyelination. Microglial nodules were present near some cells showing "severe degeneration" (neuronophagia) as depicted

16. Spielmeyer, W.: Ueber einige Beziehungen zwischen Ganglienzellveränderungen und gliösen Erscheinungen besonders am Kleinhirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **54**:1, 1920.

17. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1922, vol. 1, pp. 75 and 424.

in figure 4. Scattered, loose aggregates of microglia, interspersed with some oligodendroglia and rare polymorphonuclear cells, were present in the gray matter of the brains of 4 patients with early encephalitis (fig. 3). In the case of eleven days' duration the amount of microglia in the cortex was greatly increased. Microglial cells containing numerous small droplets of fat were arranged perpendicularly to the surface of the brain, singly or forming almost solid fields over large areas of cortex containing fairly well preserved ganglion cells. Similar diffuse collections of microglia were present in the gray matter of the lower portion of the cord. Astrocytes on the periphery of the areas of demyelination were present only in the cases of six and eleven days' duration. Small foci of marginal gliosis were seen in some of the early cases, but the case of eleven days' duration showed extensive, almost diffuse, marginal gliosis in the brain and cord.

Meninges.—Cellular infiltration of the meninges was present in 4 cases. In 3 early cases it was limited to only a few sulci of the cortex, and in the case without cerebral manifestations it was very slight. The infiltrating cells were lymphocytes, but in 1 case some polymorphonuclear forms were also present (fig. 6). In the case of eleven days' duration lymphocytic infiltration was present in the meninges on the anterior aspect of the lower part of the spinal cord.

Optic Nerves.—The optic nerves were affected only in the case of eleven days' duration. They showed diffuse, wide borders of marginal gliosis and a few small focal glial collections within the nerves. The nerves were somewhat edematous but showed no perivascular infiltration and no loss of myelin.

Our pathologic material from 7 cases covers the evolution of the lesions of measles encephalitis from those encountered in the earliest, asymptomatic stage to a full-blown, classic picture in a case of eleven days' duration.

The 3 earliest cases (the asymptomatic case, the case of one day's duration and 1 of the cases with a three days' history) showed no perivascular loss of myelin, which is generally considered to be the most characteristic feature of measles encephalitis and which is present in most cases coming to necropsy. The pathologic picture in these 3 cases consisted of lymphocytic infiltration of the walls of the veins in the gray and white matter, foci of neuronophagia, loose glial aggregates in the gray matter and cellular infiltration of the meninges. In the 4 cases with demyelination some of these features were absent, but the infiltration of the vascular walls was present in all and was more prominent in the 2 cases of three days' duration than in those with six and eleven day histories. It is therefore apparent that both infiltration of the vascular walls and demyelination are part of the same process and that

the former is the earliest pathologic lesion, which becomes less pronounced as time goes on and as degeneration of myelin sets in. In the case of eleven days' duration the vascular infiltrates could be of a different nature, as they were located near areas of softening and could be considered secondary to resorption from those areas.

Many authors consider measles encephalitis as a degenerative disease from the onset. Degeneration of myelin, when present, is undoubtedly

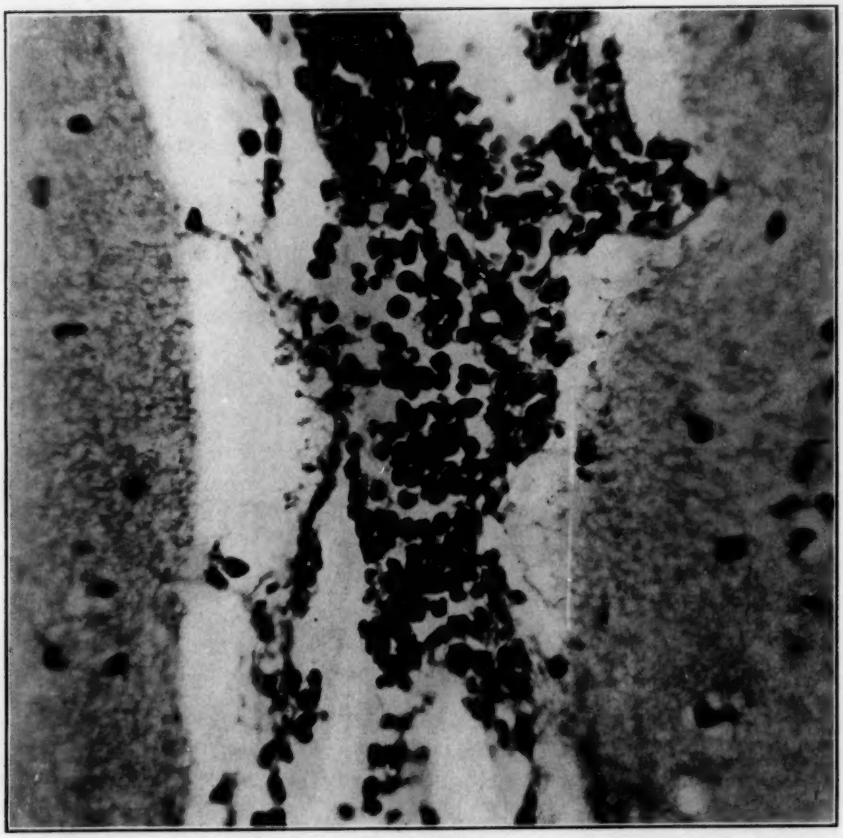

Fig. 6 (case 17).—Cellular infiltration of the meninges in encephalitis of three days' duration. Hematoxylin and eosin stain.

the most spectacular and obvious change in measles encephalitis. However, as seen from our material, it is not always present, because it was absent in 3 of our earliest cases. The changes that were common to all cases, early and late, were those of inflammation, as understood by Spielmeyer.[17] Spielmeyer's three criteria of inflammation of nerve tissue are: exudation (infiltration with cells from blood and lymph channels), alteration (degeneration) and proliferation (of local cells).

All our cases showed exudation (lymphocytic infiltration of the vascular walls was present in all cases; meningeal infiltration was seen in 4). Proliferation of glial elements was present in all, in the form of glial nodules, in the form of loose or compact aggregates in the gray matter, in the areas of demyelination or as marginal gliosis. Alteration manifested itself as "severe cellular damage" in 3 cases and as anoxemic degeneration in 5. Thus, the three postulates of Spielmeyer were fulfilled in all our cases.

We consider, therefore, that, morphologically, measles encephalitis is primarily an inflammatory disease of the central nervous system, in which degeneration of myelin develops in some cases of three days' duration, and, invariably, in all cases with a more prolonged clinical course. We are not alone in upholding the conception that measles encephalitis is of inflammatory nature, as Malamud [18] likewise considered that in the acute stage of encephalitis complicating measles the process is inflammatory.

We also think that the old, time-honored term "measles encephalitis," signifying inflammation, is fully justified and is preferable to the now popular term "measles encephalopathy" which ignores the existence of inflammatory changes in that condition.

In making this statement on the inflammatory character of measles encephalitis we refer, of course, only to the morphologic features of the evolution of the cerebral lesion in measles, without going into the pathophysiologic mechanism of the degeneration of myelin, which is a problem not for a clinician or morphologist but for an experimental worker.

CLINICAL MANIFESTATIONS

Age.—Measles is essentially a disease of childhood, and the complication of encephalitis also occurs most frequently in this period. However, adults with measles seem no less prone to an associated encephalitis. In our series of cases, 94.5 per cent of patients were not more than 14 years of age. Only 4 patients were over 21. The age of our youngest patient was 14 months. Our oldest patient was 35 years of age.

Sex.—Of our patitents 58.9 per cent were female.

Incidence.—Ford,[2] quoting Boenheim, stated that the incidence of nervous complications of measles was 0.4 per cent. However, the incidence of encephalitis alone in Boenheim's series was 0.1 per cent. Peterman and Fox,[3] citing figures for the Milwaukee measles epidemic of 1931-1932, and Hoyne's report [19] from Chicago hospitals during the

18. Malamud (footnotes 10 and 11).

19. Hoyne, A. L.: Measles in 1938: Analysis of Four Hundred Cases—Twenty-Eight Instances of Encephalitis, Illinois M. J. **76**:136 (Aug.) 1939.

epidemic of 1937-1938, show that the incidence of encephalitis is slightly less than 1 case per thousand.

Time of Onset.—The relation of the onset of encephalitis to the first appearance of the rash is shown in figure 7. It will be noted that the vast majority of cases of encephalitis complicating measles occurred after the appearance of the rash. It may, however, on rare occasions, precede the rash or be coincident with it. Of our cases 86.1 per cent occurred between the second and sixth posteruptive days. Occurrence on the third posteruptive day was most frequent. The longest interval between the appearance of the rash and the onset of the encephalitis was fourteen days.

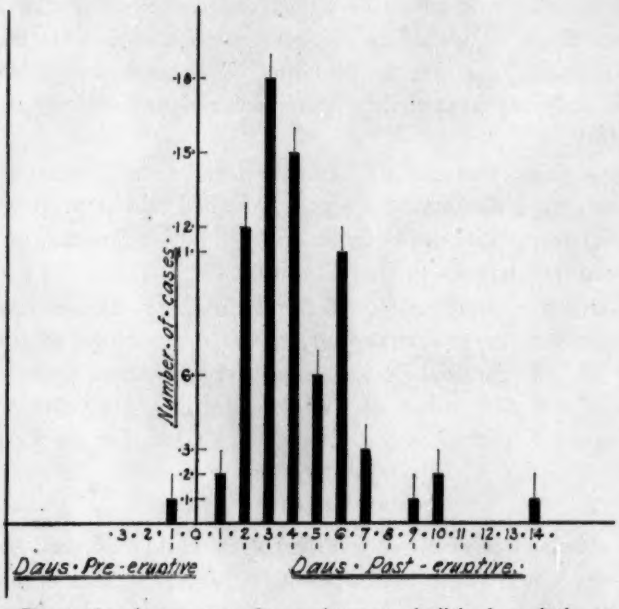

Fig. 7.—Chart showing onset of measles encephalitis in relation to the first appearance of the rash.

Mode of Onset.—The disease was often ushered in dramatically, with coma or convulsions, or both. This acute mode of onset occurred in 40.5 per cent of our cases. Typically, a child who was recovering from measles and showed measles staining and a normal temperature was suddenly, about three to six days after the first appearance of the measles rash, taken acutely ill with coma and convulsions and a high fever. The temperature commonly reached 104 or 105 F. or even higher. The pulse was rapid, and the respirations were often irregular and at times Cheyne-Stokes in character. Neurologic examination most commonly revealed stiffness of the neck and positive Kernig, Brudzinski and Babinski signs. This clinical picture reflected an acute meningo-encephalitic insult.

In other cases, the mode of onset was more gradual, and the predominating symptoms were drowsiness and irritability. Vomiting and headache were not infrequently present. In 4 cases (5.4 per cent) the illness commenced with excitement and delirium. In 2 cases (2.7 per cent) the sensorium remained clear throughout, and the main symptoms were weakness and sensory disturbances of the lower extremities associated with urinary retention. These latter 2 cases were instances of measles myelitis. Thus, myelitis alone was a rare complication of measles. More commonly, we dealt with encephalomyelitis in which the myelitic manifestations were mild and rather submerged by the more prominent encephalitic component.

Temperature.—The temperature was nearly always elevated. The temperature curve pursued no characteristic course. In some instances it returned to normal within twenty-four hours. In other cases it remained elevated for a week or longer. Elevation was intermittent or remittent in character. The fever was occasionally due, wholly or in part, to a coexisting complication of measles, such as otitis media or pneumonia. In 3 cases there was no elevation in temperature. Hyperpyrexia, associated with coma and convulsions and death within twenty-four hours, occurred in 4 cases.

Clinical Course.—Since the pathologic process is diffuse and varies greatly, as regards both the area involved and the intensity of the insult, the clinical course of the disease was likewise extremely variable, and almost every sign and symptom indicative of involvement of the central nervous system was encountered (table 2). Moreover, in the acute phase of the disease, while the offending agent is still active, the clinical picture may change radically from day to day and even from hour to hour. As the early acute phase of the illness subsided, the extent of the neurologic involvement, when present, became more apparent. Some patients showed evidence of extensive damage indicative of multiple and diffuse lesions of the central nervous system. Others were more fortunate and escaped with single focal lesions. We wish to emphasize the almost constant occurrence of mental symptoms in the early phase of the disease. Consciousness was nearly always disturbed to some degree and varied from drowsiness to stupor and coma. Dramatic shifts in the state of consciousness were frequently observed. Patients who were mildly drowsy were seen suddenly to lapse into coma. On the other hand, we not infrequently saw patients whose illness commenced with convulsions and deep coma who, when seen the next morning, were alert and cooperative. Personality changes in the acute stage were common and consisted most frequently of restlessness and irritability. A few patients were extremely noisy and talkative and would giggle in a silly fashion on the slightest provocation. Psychotic reactions

TABLE 2.—*Signs and Symptoms of Measles Encephalitis in 74 Patients During Period of Hospitalization*

Signs and Symptoms	Number of Cases
Reflexes	
Deep reflexes exaggerated	31
Deep reflexes absent	15
Deep reflexes sluggish	8
Abdominal reflexes absent	42
Abdominal reflexes sluggish	4
Babinski's sign	27
Ankle clonus	15
Meningeal irritation	
Stiffness of neck	39
Kernig's sign	37
Brudzinski's sign	12
Headache	8
Vomiting	17
Sensorium	
Drowsiness	38
Stupor	17
Apathy	15
Coma	20
Irritability	36
Cerebral cry	6
Mental confusion	18
Delirium	4
Restlessness	7
Negativism	1
Psychosis	2
Mental retardation	2
Excessive laughter	3
Motor power and coordination	
Spastic paraplegia	4
Flaccid paraplegia	3
Hemiplegia	1
Myoclonia	9
Convulsions	30
Tremor of hands	6
Staggering gait	1
Intention tremor	2
Choreiform movements	1
Sensation	
Abdominal pain	5
Pain in extremities	2
Hypesthesia with sensory level	3
Hyperesthesia	11
Cranial nerves	
Anisocoria	4
Fixed dilation of pupils	6
Sluggish reaction of pupils to light	5
Absence of reaction of pupils to light	4
Congestion and blurring of optic disks	2
Optic atrophy	2
Ophthalmoplegias	2
Paralysis of the facial nerve	8
Nystagmus	7
Blurring of vision	1
Muscle tone	
Hypotonus	5
Hypertonus	7
Bladder and bowel	
Urinary retention	8
Urinary incontinence	12
Fecal retention	1
Medulla	
Cyanosis	4
Irregular respirations	4
Hyperpyrexia	4
Miscellaneous	
Aphasia	1
Slurred speech	2
Corneal ulcer	1
Oculogyric crises	1
Bradycardia	1
Facial masking	2
Drooling from mouth	1

were observed and consisted mainly of mental confusion, delirium, hallucination, negativism and occasional bizarre regressive behavior. Convulsions were tonic or clonic, generalized or jacksonian. Myoclonic twitching of muscles was observed in 9 cases and most frequently involved the muscles of the face and of the upper extremity. Tremor of the hands occurred in 6 cases. Intention tremor was elicited in 2 cases. Urinary retention was present in 8 cases. Abdominal pain was a major symptom with 5 children and was usually associated with urinary retention. Pain in the extremities was a complaint in only 2 instances.

Neurologic examination in the acute phase of the illness revealed signs indicative of meningeal irritation and increased intracranial pressure. In addition, many cases also showed Babinski's sign. The reflexes were variable. The deep tendon reflexes were most commonly exaggerated, but in several instances they were absent or sluggish. Absence of the superficial abdominal reflexes was the most constant finding. Ankle clonus was a fairly common observation. Inequality of the size of the pupils was noted in 4 cases. Fixed dilatation of the pupils was seen in 6 patients. A sluggish reaction of the pupils to light was occasionally seen. Blurring of the disks was found in 2 cases, and optic atrophy was also noted in 2 instances. In 1 case there was a corneal ulcer, due probably to a direct involvement of the gasserian ganglion. Two patients showed paralysis of the lateral rectus muscle of the eye. Nystagmus was observed in 7 cases. The seventh cranial nerve was most commonly involved (8 cases). Facial masking was observed in 3 patients. Oculogyric crises occurred in 1 case. Impairment of the speech mechanism was occasionally seen. Four patients had spastic paraplegia. A staggering gait was noted in 1 case. Hemiplegia occurred in 1 patient. Psychoses and personality changes were not infrequent sequelae. The final clinical outcome was often in doubt until considerable time had passed.

Four typical cases are presented.

REPORT OF CASES

CASE 48.—G. K., a 6 year old white boy, was admitted to Willard Parker Hospital on May 23, 1943, because of high fever and a state of stupor. The child was first seen by his private physician on May 21, at which time he had a generalized maculopapular rash, which included the face, conjunctivitis and coryza. Koplik spots were noted on the buccal mucosa. The temperature was 101 F. Two days after the first appearance of the rash, the child became increasingly drowsy, vomited and lapsed into a semicomatose state.

Examination on admission revealed an acutely ill child who was in a state of coma. The temperature was 104 F., and a morbilliform rash was noted over the face, body and extremities. Neurologic examination showed a bilateral Babinski sign, hypoactive deep reflexes, stiffness of the neck and a positive Kernig sign. The superficial abdominal reflexes were absent. The remainder of the examination

revealed nothing abnormal. Shortly after admission, the child had several tonic and clonic generalized convulsions. A spinal tap on the day of admission showed the fluid to be clear in appearance, with an initial pressure of 180 mm. of water. It had 165 cells per cubic millimeter, with 80 per cent lymphocytes, and 106 mg. of protein and 88 mg. of sugar per hundred cubic centimeters. The blood count revealed 3,900,000 red blood cells per cubic millimeter, hemoglobin concentration of 70 per cent (Sahli) and 12,000 white blood cells, with 71 per cent polymorphonuclear cells. The urine showed no abnormality.

On May 24, convulsions continued. They were controlled with amobarbital sodium N.N.R. ("amytal sodium") intravenously and 4 cc. of a 25 per cent solution of magnesium sulfate intramuscularly. On May 25, bilateral ankle clonus was elicited, and there was no clearing of consciousness. The respirations were feeble and irregular, and a considerable accumulation of mucus was present in the posterior pharynx. Lumbar puncture was repeated and showed clear fluid, with 190 cells per cubic millimeter and a differential count of 90 per cent lymphocytes, and of 56 mg. of protein and 99 mg. of sugar per hundred cubic centimeters. On May 26, it was noted that the child was still in profound stupor; the pupils were contracted; there was slight nuchal spasm and a positive Kernig sign. The deep reflexes were present but hypoactive bilaterally, and the superficial reflexes were absent. It was felt that the clinical picture was that of a severe form of measles encephalitis. The prognosis was regarded as poor as far as the patient's future mental state was concerned. The nutrition was supported by daily infusions of 5 per cent dextrose in isotonic sodium chloride solution and of isotonic chloride solution and by transfusions of whole blood.

On May 29, the child began to react from his comatose state for the first time. He surveyed his surroundings and was able to respond to simple questions. He took small sips of water by mouth. His temperature was 102 F. On June 5, he was able to move all his extremities. His vocabulary had increased, and he asked for something to eat. He improved steadily, and, on June 12, his mental state was normal for the first time. Neurologic examination at this time showed the following: The pupils were equal in size and shape and reacted to light and in accommodation; the superficial abdominal reflexes were present; a positive Babinski sign was not elicited; the deep reflexes were equal and active bilaterally; there was no nuchal spasm or Kernig sign, and no paralysis was noted. The patient's temperature had remained elevated for two weeks after his admission, with a mean level or 103 F.

He was discharged from the hospital on August 25, with no evidence of physical or mental sequelae. He was seen at the follow-up clinic on September 14. His personality and behavior were normal at that time, and neurologic examination showed no abnormality. He failed to keep his later appointments with the follow-up clinic.

CASE 55.—L. W., a 9 year old white girl was admitted to the Willard Parker Hospital on Jan. 7, 1944. On Dec. 31, 1943, she had a running nose and a cough. On Jan. 1, 1944, she was feverish, and on January 3 a rash was noticed on her face, which soon spread to her trunk and extremities. The rash was maculopapular in character. Koplik spots were noted on the buccal mucous membrane. On January 7, the child became apathetic and drowsy and was brought to the Willard Parker Hospital.

On admission, examination revealed a fairly well nourished 9 year old child who appeared completely apathetic but would utter a weird cry on occasion for no apparent reason. She was observed to stare vaguely into space without any emotional reaction. Her temperature was 103 F. and typical postmeasles staining

was observed. Her pupils reacted sluggishly to light. There was paralysis of the left facial nerve, a positive Kernig sign and a positive Brudzinski sign. The deep reflexes were present but sluggish, and the superficial reflexes were absent. A lumbar puncture was performed on admission. Examination of the spinal fluid revealed that the fluid was clear, with 150 cells per cubic millimeter, 90 per cent lymphocytes and 68 mg. of protein and 83 mg. of sugar per hundred cubic centimeters. Smear and culture did not show micro-organisms. Her nutrition was supported by parenteral administration of fluids.

On January 8, the child showed decided improvement. She reacted from her apathy and now appeared moderately alert, but remained extremely irritable and hyperesthetic. On January 10, she sat up and fed herself. No abnormal neurologic signs were present. The superficial abdominal reflexes were now equal and active. On January 13, she spoke intelligently and was alert and well oriented; according to her parents, her personality returned to normal. She was seen on November 14 in the follow-up clinic. She was reported as doing well in school; she showed no personality deviations, and the neurologic examination showed no abnormalities. She was seen again on Aug. 5, 1946, in the follow-up clinic. Results of the neurologic examination were again completely normal. Her mother stated, however, that she had been quite irritable since her last examination in 1944 and would scream and shout when told to do something to which she objected.

CASE 74.—A. G., an 8 year old white boy, was admitted to the Willard Parker Hospital on Aug. 8, 1946. On July 29, cough, coryza and conjunctivitis were noticed by his private physician. Koplik spots were seen on the buccal mucous membrane on August 1. On August 4, the child had a generalized maculopapular rash and a temperature of 104 F. His fever subsided, and his clinical course was uneventful until the evening of August 8. At this time he vomited, appeared lethargic and disoriented and was brought to the Willard Parker Hospital.

Examination on admission revealed a well developed 8 year old child who appeared somewhat apathetic and confused. The temperature was 103.8 F. A receding measles rash was observed. The pharynx was slightly injected. Otoscopic examination showed normal landmarks and a light reflex bilaterally. Neurologic examination showed definite nuchal rigidity and positive Brudzinski, Kernig and Babinski signs bilaterally. The deep reflexes were present but sluggish. Examination of the spinal fluid on admission showed 600 cells per cubic millimeter, 60 per cent polymorphonuclear cells and 178 mg. of protein and 91 mg. of sugar, per hundred cubic centimeters. Smear and culture of the spinal fluid were negative for micro-organisms. Examination of the urine showed no abnormality. A blood count revealed 11,000 white blood cells, with a differential count of 51 per cent polymorphonuclear cells and 49 per cent lymphocytes. The hemoglobin concentration was 11.25 Gm., red blood cells numbered 4,000,000. Roentgenograms of the chest on August 10 was reported as showing only slight perihilar thickening inferiorly.

On August 10 the child had urinary retention with overflow incontinence. The bladder was percussed to 3 fingerbreadths above the symphysis pubis. The child was drowsy and quite irritable and complained of headache in the occipital region. On the evening of August 10 his temperature rose to 104 F. and his cough became more pronounced. The percussion note was impaired over the lower lobe of the right lung and crepitant and medium-pitched rales were heard over this area. Roentgenographic examination of the chest on August 10 was reported as showing a small patch of consolidation over the lower lobe of the right lung. He was given 25,000 units of penicillin every three hours. On August 11 his temperature dropped to 99.6 F., and his general condition was much improved. Lumbar puncture was

repeated and showed 15 cells per cubic millimeter, 100 per cent lymphocytes and 89 mg. of protein and 64 mg. of sugar, per hundred cubic centimeters. On August 12 his temperature was normal, but he remained apathetic and drowsy. Overflow incontinence continued and an indwelling catheter was inserted. There was no nuchal rigidity but moderate nuchal spasm was present. Kernig and Brudzinski signs were not elicited. The knee jerks were now more active and were equal bilaterally. The superficial abdominal reflexes were still absent. On August 13 moderate abdominal distention was noted. On August 14 he was alert and cooperative but complained of pain in both legs. Neurologic examination revealed spastic paraplegia with a vague level of hypesthesia extending to the tenth dorsal neural segment on the right and to the twelfth segment on the left. Urinary retention with overflow incontinence was still present. A positive Babinski sign, ankle clonus and exaggerated knee jerks were elicited bilaterally. It was felt that these features represented myelitis superadded to the patient's encephalitis. The outlook appeared to be favorable in view of the good mental state of the patient at the time. On August 20 a moderate degree of improvement of his motor power in the lower extremities was evident. On September 4 he was transferred to another institution. We were informed that he improved steadily. On Feb. 2, 1947, neurologic examination showed normal knee jerks with absence of spasticity of the lower limbs. The child was able to walk quite well. The superficial abdominal reflexes were, however, still absent, and there was a positive bilateral Babinski sign. Return of sensation to pain and touch was almost complete.

CASE 43.—N. B., a 6 year old white girl, was admitted to the Willard Parker Hospital on June 26, 1941. There was a history of cough, coryza, conjunctivitis and elevated temperature on June 22. A rash first appeared on June 24, which involved the face and soon spread to the trunk and extremities. The rash was maculopapular in character. Koplik spots were noticed on the buccal mucosa by her private physician on June 23. On June 26 she showed increasing lethargy and extreme irritability.

Examination on admission revealed a 6 year old female child who was lethargic and very irritable. A fading maculopapular rash was noted. Her temperature was 103 F., the pulse rate was 154 and respiratory rate 34 per minute. The pharynx showed moderate injection. There was definite nuchal rigidity. The pupils reacted sluggishly to light. A positive Kernig sign was present. The superficial abdominal reflexes were absent. The knee jerks and ankle jerks were present bilaterally, and a bilateral positive Babinski sign was elicited. The bladder was percussed 3 inches (7.6 cm.) above the pubis. Pronounced tachycardia was present, but the heart sounds were of fair quality. There were no murmurs, and the apex beat was in the fifth intercostal space within the midclavicular line. The remainder of the physical examination showed nothing abnormal. A lumbar puncture was done on admission. Examination of the spinal fluid showed cloudy fluid, with 1,670 cells per cubic millimeter, 90 per cent polymorphonuclear cells and 172 mg. of protein and 54 mg. of sugar, per hundred cubic centimeters. Smear and culture of the spinal fluid did not show micro-organisms. The urine showed no abnormality. A blood count revealed 26,500 white blood cells per cubic millimeter, with 81 per cent polymorphonuclear cells and a moderate shift to the left, 4,300,000 red blood cells per cubic millimeter and a hemoglobin concentration of 75 per cent. The Wassermann reaction was negative. On June 28 the lethargy deepened and the child was in a semicomatose state. The temperature was 104 F. Lumbar puncture was repeated on June 28, and the fluid showed 240 cells per cubic millimeter, 75 per cent of which were now lymphocytes, 50 mg. of protein and 59 mg. of sugar, per hundred cubic centimeters. Smear and culture were again negative.

She was given infusions of dextrose and saline solution for supportive therapy. Thiamine hydrochloride, 30 mg., and a vitamin C preparation, 100 mg., were given daily subcutaneously. She was catheterized as needed. The temperature was high and remittent during the first week of hospitalization. Roentgenograms of the chest on June 20 showed a few small patches of consolidation in the upper part of each lung. Sulfathiazole, 0.5 Gm. every four hours, was administered. A repeated roentgenographic examination of the chest on July 9 showed no consolidation of either lung. The child remained semicomatose during the first week of her stay in the hospital. During the second week of hospitalization, she was in a state of severe apathy and semicoma and was completely unaware of her surroundings. She was unable to recognize her parents. Examination on July 7 revealed that the child was semicomatose and difficult to arouse. Her pupils were 5 mm. in diameter and were fixed to light. Examination of the fundi showed definite and advanced optic neuritis. There was no reaction on her part to a bright light or flash. Her corneas were anesthetic, and corneal ulcer was seen in the left eye. No other cranial nerve abnormalities were noted. The deep reflexes were absent, as were the superficial abdominal reflexes. The Babinski sign was present bilaterally. Lumbar puncture was repeated on July 14. Examination of the spinal fluid showed 4 cells per cubic millimeter and 45 mg. of protein and 75.6 mg. of sugar, per hundred cubic centimeters. An electrocardiogram was made on July 14, which showed that the P-R interval was 0.12 second wide and the QRS interval, 0.05 second wide. The auricular rate and the ventricular rate were 112 per minute, with no axis deviation.

The patient was hospitalized for seven weeks. She never responded during her stay in the hospital. She was given oxygen, infusions of dextrose solution, chemotherapeutic agents and whole blood transfusions. She was discharged to her home on August 21, where she was taken care of for two years. There was no improvement during this period. She was then transferred to a psychiatric institution, where she remains today. We have been informed that she functions at an almost vegetative level. She is unable to talk or walk and cannot feed herself. She can sit up when propped against a pillow. She has urinary incontinence.

LABORATORY FINDINGS

Spinal Fluid.—A spinal tap was done at least once in all cases but 2. The results of the spinal fluid examinations are shown in table 3. The fluid was clear in the great majority of instances and was frequently under moderately increased pressure. A moderate increase in the number of white cells was the commonest abnormal finding. The pleocytosis was under 100 cells per cubic millimeter in 47 cases (66.2 per cent). A cell count of 500 or more was distinctly unusual and occurred in only 4 cases. The highest cell count in our series was 1,670 cells. Eight cases had a normal spinal fluid cell count. The differential cell count most usually showed a definite predominance of lymphocytes, but in 4 cases the polymorphonuclear cells predominated. In these cases, on repeated lumbar puncture, a drop in cell count with a shift toward a lymphocytic preponderance became apparent. There was a moderate increase in the protein content in the majority of cases. The sugar level was normal or elevated in all cases. A persistent depression of the

TABLE 3.—*Spinal Fluid Findings and Blood Counts in Measles Encephalitis*

	Spinal Fluid								Blood	
Case No.	Appearance	Spinal Fluid Cell Count	Lymphocytes, %	Albumin	Globulin	Total Protein, Mg./100 Cc.	Reaction for Sugar	Sugar, Mg./100 Cc.	White Blood Cell Count	Polymorphonuclear Cells, %
1	Clear	5	100	+	+	....	+++	....	.....	..
2	Clear	540	98	+	+	....	+++	....	8,750	84
3	Clear	0	0	±	±	....	+++	....	5,800	82
4	Clear	460	96	++	++	....	+++	....	.....	..
5	Clear	25	100	+	+	....	+++	....	.....	..
6	Clear	75	96	±	±	....	+++	....	8,600	52
7	Clear	20	90	+	+	....	+++	....	.....	..
8	Clear	140	94	+	+	....	+++	....	9,850	67
9	Clear	45	100	+	+	....	+++	....	8,850	86
10	Clear	15	100	±	±	....	+++	....	14,600	69
11	Clear	130	92	+	+	....	+++	....	.....	..
12	Clear	35	100	+	+	....	+++	....	13,500	80
13	Clear	10	100	+	+	....	+++	....	10,000	61
14	Clear	30	100	+	+	....	+++	....	..	..
15	Clear	60	100	+	+	....	+++	....	.....	..
16	Clear	15	100	+	+	....	+++	....	.....	..
17	Clear	360	96	+	+	....	+++	....	.....	..
18	Clear	80	96	+	+	....	+++	....	9,250	66
19	Clear	55	91	+	+	....	+++	....	19,250	75
20	Clear	20	100	±	±	....	+++	....	17,800	85
21	Clear	110	91	+	+	....	+++	....	5,800	64
22	Blood tinged	15	96	±	±	....	+++	....	6,200	43
23	Clear	25	100	±	±	....	+++	....	.....	..
24	Clear	85	100	+	+	....	+++	....	8,500	82
25	Clear	20	100	+	+	....	+++	....	11,900	80
26	Clear	140	80	+	+	....	+++	....	22,500	85
27	Clear	5	100	..	..	14.8	...	71.9	20,000	68
28	Clear	5	100	..	..	12.7	...	85.0	9,600	78
29	Clear	20	80	..	..	66.4	...	97.0	27,000	19
30	Clear	100	98	..	..	77.3	...	60.6	17,000	80
31	Clear	285	85	..	..	27.0	...	145.0	12,350	65
32	Clear	25	100	..	..	32.0	...	47.0	.....	..
33	Clear	300	95	..	..	126.0	...	65.0	9,050	51
34	Clear	265	70	..	..	53.0	...	46.6	10,100	57
35	Clear	15	100	..	..	27.0	...	70.0	12,500	80
36	Clear	115	65	..	..	54.0	...	71.0	14,500	56
37	Spinal tap not done									
38	Clear	80	100	..	..	13.0	...	58.6	.....	..
39	Clear	20	100	..	..	33.0	...	118.0	7,250	61
40	Clear	50	80	..	..	....	...	....	7,650	58
41	Clear	80	98	..	..	60.0	...	192.0	19,100	82
42	Clear	75	95	..	..	70.0	...	74.0	16,000	80
43	Cloudy	1,670	90P	..	..	172.0	...	54.0	26,500	81
44	Clear	60	100	..	..	62.0	...	62.0	18,800	88
45	Clear	410	70	..	..	140.00	...	80.0	10,300	80
46	Clear	70	95	..	..	143.0	...	138.0	9,500	82
47	Clear	60	98	..	..	59.0	...	143.0	15,000	56
48	Clear	165	80	..	..	106.0	...	88.0	12,000	71
49	Clear	42	85	..	..	46.0	...	78.0	.....	..
50	Clear	0	0	..	..	12.0	...	73.0	.....	..
51	Clear	0	0	..	..	29.0	...	64.0	5,500	70
52	Clear	20	100	..	..	34.0	...	65.0	12,500	74
53	Clear	110	91	..	..	103.0	...	65.0	.....	..
54	Clear	100	96	..	..	69.0	...	117.0	18,300	67
55	Clear	150	90	..	..	68.0	...	88.0	.....	..
56	Clear	90	100	..	..	110.0	...	63.0	7,200	65
57	Clear	50	90	..	..	36.0	...	218.0	12,400	75
58	Clear	65	60P	..	..	49.0	...	160.0	.....	..
59	Opalescent	450	95	..	..	105.0	...	100.0	27,500	85
60	Clear	0	0	..	..	11.0	...	82.0	9,100	67
61	Clear	35	89	..	±	....	...	91.0	8,900	60
62	Clear	10	100	..	..	36.0	...	82.0	.....	..
63	Clear	275	85P	..	..	68.0	...	64.0	.....	..
64	Clear	85	100	..	..	79.0	...	74.0	.....	..
65	Clear	20	100	..	..	66.0	...	67.0	.....	..
66	Clear	120	92	..	..	66.0	...	77.0	.....	..
67	Clear	50	95	..	..	41.0	...	78.0	9,700	78
68	Clear	50	100	..	..	40.0	...	61.0	.....	..
69	Clear	0	0	..	..	30.0	...	111.0	.....	..
70	Spinal tap not done									
71	Clear	156	90	..	..	70.0	...	76.0	.....	..
72	Cloudy	1,470	95	..	..	88.0	...	82.0	.....	..
73	Clear	115	95	..	..	96.0	...	84.0	.....	..
74	Cloudy	600	60P	..	..	178.0	...	91.0	11,000	51

The ± sign indicates normal, + a slight increase, ++ a moderate increase and P polymorphonuclear cells.

sugar content was not observed. Smears and cultures for micro-organisms were negative in all cases.

Blood Picture.—The white cell count was performed in 45 cases (table 3). The leukopenia and lymphocytosis of measles were replaced in most instances by a moderate leukocytosis, with a predominance of polymorphonuclear cells.

DIFFERENTIAL DIAGNOSIS

Meningitis, poliomyelitis, subarachnoid hemorrhage, drug and other forms of toxic encephalopathy, other encephalitides, brain tumor and meningism may at times be confused with measles encephalitis. Tuberculous meningitis, with drowsiness or stupor, may simulate closely measles encephalitis. It is also well to remember that measles may activate a tuberculous process. In a case in which the diagnosis was measles encephalitis, necropsy showed multiple tuberculomas of the brain

TABLE 4.—*Follow-Up Findings in 33 Cases of Measles Encephalitis*

No abnormality	13
Psychosis	4
Mental retardation	3
Hyperreflexia	3
Paralysis	3
Irritability	3
Tics	2
Obesity	1
Restlessness	1
Temper tantrums	1

and tuberculous meningitis. It is also necessary to point out that the presence of measles encephalitis may at times be unsuspected. In the differential diagnosis careful attention must be paid to the history and the results of examination of the spinal fluid. The outstanding differential point is the occurrence of clinical manifestations of encephalitis in chronologic association with an attack of measles.

OUTCOME

In our series of 74 patients with measles encephalitis, 7 died, a mortality rate of 9.5 per cent. In each of these persons, death occurred within the first week of illness. Four of the patients also had hyperpyrexia. The 3 other patients who died had pulmonary complications. Forty-two patients (56.8 per cent) were discharged from the hospital without any neurologic or other detectable abnormality. The average number of days of hospitalization for the latter group of patients was 27.3.

Our follow-up study consisted of observations on 33 patients, which are presented in table 4. The shortest follow-up period was four months,

and the longest period was ten years. For 28 of our patients, the follow-up period exceeded two years. Thirteen of the 33 patients escaped without any residual symptoms. In the remaining 20 patients some sequelae were noted, the commonest of which were psychosis, mental retardation, paralysis and personality deviation.

In the follow-up study it was of particular interest to note the outcome in those patients who on discharge from the hospital showed no abnormalities. Nineteen patients fell into that group. The shortest follow-up period in this group was two and one-half years, and the longest period was eight and one-half years. The results of that investigation are shown in table 5. No abnormality was discovered in 11 patients. The other 8 patients showed only relatively minor disturbances that were considered as probably being causally related to measles encephalitis. The deviations were most commonly in the field of behavior. We agree with Litvak and associates [5] that the neurologic sequelae

TABLE 5.—*Follow-Up Results on 19 Patients Who Were Discharged from the Hospital Without Residual Symptoms*

No abnormality	11
Hyperreflexia	3
Tics	2
Obesity	1
Emotional instability	1
Irritability	1

of measles encephalitis tend to disappear with the passage of time. We are not, however, certain that the deviations in behavior are directly due to the encephalitis, for some of them could be explained perhaps equally well on the basis of parental attitudes, such as maternal overprotection after an illness, or other environmental influences.

PROGNOSIS

The prognosis of measles encephalitis should always be guarded. We found hyperpyrexia to be an unfavorable sign. Age and sex seem to bear no relation to the prognosis. Laboratory data were of no aid in prognosis. We were unable to find any correlation between the severity of the encephalitis and the time of its development in relation to the rash. Patients who were in coma for a prolonged period were prone to have pneumonia as an added complication. A prolonged state of coma was, as a rule, a poor prognostic sign, although we observed several patients who were in a comatose state for a week and who eventually made a complete recovery with no residual symptoms. Persistent and prolonged apathy, often associated with a cerebral cry, in which the patient seemed out of contact with his environment, was an

unfavorable prognostic sign. An onset with coma and convulsions did not necessarily indicate a poor prognosis. The occurrence of encephalitis bore no relation to the severity of the measles. Similarly, the intensity of the encephalitis seemed unrelated to the severity of the primary disease.

TREATMENT

One must be cautious in ascribing good results in measles encephalitis to any particular therapeutic agent, for dramatic improvement occurs frequently without any specific therapy. We used human measles immune serum N. F., human pooled plasma and blood transfusions without any apparent beneficial effect. We employed human gamma globulin for only 1 patient, and the outcome in this instance was favorable. This agent deserves further clinical trial for its proper therapeutic evaluation.

Headache was frequently alleviated by lumbar puncture. Convulsions were controlled by ether given by the open drop method, by amobarbital sodium intravenously and by magnesium sulfate intramuscularly. Nursing care was particularly emphasized for patients who were in coma. Aspiration of vomitus was carefully guarded against, and an airway was constantly provided. Supportive therapy and fluid and electrolyte balance were maintained by infusions of 5 per cent dextrose solution, isotonic sodium chloride solution and Hartmann's solution. Gavage feeding was employed for patients who refused food and for those who remained in stupor or coma for a prolonged period. Bulbar symptoms were treated by elevation of the foot of the bed, nasopharyngeal suction, parenteral administration of fluids and withholding of everything by the oral route. Oxygen was administered to patients with complicating pneumonia or cyanosis or irregular, embarrassed respirations. Excitement, restlessness and sleeplessness were controlled by barbiturate derivatives. Pyogenic complications, such as pneumonia, and otitis media were treated with the sulfonamide drugs and penicillin, when these agents became available.

SUMMARY AND CONCLUSIONS

1. This report is based on 74 cases of measles encephalitis seen at the Willard Parker Hospital from 1936 to 1946.

2. The encephalitis of measles is morphologically an inflammatory disease. The early lesions are lymphocytic infiltration of the walls of small veins in the gray and white matter of the brain, meningeal cellular infiltration, degeneration of ganglion cells and microglial proliferation. They may be present before the clinical evidence of encephalitis becomes manifest. Perivascular loss of myelin is a later, degenerative manifestation developing after three days of clinical encephalitis.

3. Measles encephalitis, like measles, is primarily a disease of childhood, although persons of any age may be affected.

4. The onset most commonly occurs between the second and sixth day after the first appearance of the rash, although it may occur before the rash or as late as three weeks after the first appearance of the rash.

5. High fever, coma, convulsions, drowsiness and irritability are common symptoms at the onset. Excitement and delirium are less frequent. On rare occasions, the sensorium remains intact, and the main symptoms are weakness and sensory disturbances of the lower extremities, associated with urinary retention. These are instances of measles myelitis. Two such cases are recorded in our series.

6. The commonest physical findings in the acute stage of the disease are those indicative of meningeal irritation and increased intracranial pressure. Changes in the reflexes are frequently observed. Absence of abdominal reflexes is a frequent finding.

7. The clinical course of measles encephalitis is extremely variable, and almost any sign and symptom indicative of involvement of the central nervous system may be encountered. The residual damage may be most intense in the cerebrum, cerebellum, basal ganglions, midbrain, pons, medulla or spinal cord, and the clinical picture will vary accordingly.

8. The spinal fluid nearly always shows some abnormality. There is usually an increased number of cells, which are predominantly lymphocytes. The protein content is usually elevated. The cell count may occasionally be normal. The spinal fluid findings are of no prognostic significance. A normal spinal fluid may occur even in fatal cases.

9. The prognosis should always be guarded.

10. In our material, the mortality rate of measles encephalitis is 9.5 per cent. Forty per cent of cases may escape without sequelae. The commonest sequelae are psychosis, mental retardation, paralysis and personality deviation.

11. Treatment is entirely symptomatic. Human gamma globulin deserves further clinical trial for its therapeutic evaluation in this disease.

Miss Gladys Haber prepared the histologic material for this study.

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ELECTROLYTE BALANCE STUDIES ON PREMATURE INFANTS ON A DIET OF EVAPORATED MILK

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IN A RECENT paper, Darrow and his co-workers [1] have discussed the production of acidosis in premature infants by the feeding of an unmodified protein milk powder. In this report the authors demonstrated that the excess of chloride over sodium in the protein milk is eliminated with difficulty and that its excretion is attended with a loss of sodium from the body. Concentrations of serum chloride were found elevated, concentrations of serum sodium and bicarbonate lowered and the p_H depressed. The confirmation and extension of this work of Darrow were planned by us as part of an investigation of the water and electrolyte metabolism in premature and full term infants. As a base line for the investigation of powdered protein milk, preliminary studies were carried out on premature infants on a diet of diluted evaporated cow's milk. These studies included determinations of electrolyte balances, acid-base partitions in the urine and serum electrolyte concentrations. The observations in this preliminary exploration are considered interesting and significant enough to warrant a separate report in this paper. The succeeding paper [2] is concerned with the results of balance studies and serum analyses on infants on the powdered protein regimen and the role of the kidneys in the production of acidosis.

METHOD AND PLAN OF STUDY

Male premature infants were chosen for the experiments because of the convenience in collecting the urine. The babies ranged in age from 6 to 38 days and in weight from 1,700 to 2,090 Gm. They were kept in an environmental temperature of about 78 F., with a relative humidity of about 50 per cent. They showed no obvious perspiration. The urine-collecting apparatus consisted of a cut-off, thin-walled condom or finger cot attached by a small piece of glass tubing to a rubber

From the Hektoen Institute for Medical Research and the Children's Division of the Cook County Hospital.

1. Darrow, D. C.; Da Silva, M. M., and Stevenson, S. S.: J. Pediat. **27**:43, 1945.

2. Hoffman, W. S.; Parmelee, A. H., and Grossman, A.: Am. J. Dis. Child., to be published.

tube which extended into a small bottle. The bottle contained a layer of toluene and, though stoppered, allowed the escape of air. The apparatus was autoclaved daily and was attached and maintained under septic conditions. The proximal end was held in place by adhesive tape. For the balance studies, the specimens of urine for the three day period were mixed, and aliquots were used for analyses. For the acid-base partition studies on the urine, analyses were carried out on each twenty-four hour sample.

Stools were collected for three day periods, and aliquots of the homogenized samples were taken for the mineral analyses. Milk analyses were made on aliquots of the prepared formulas for one day. Such a formula usually consisted of evaporated milk diluted with an equal quantity of distilled water and containing 5 Gm. of "dextri-maltose." The caloric intake was about 120 calories per kilogram of body weight and was constant for each infant during each period of study. For the analysis of powdered protein milk, an aliquot of the prepared suspension of the protein milk powder in water was used. Fifteen sets of analyses were made, and the averages of these were taken as the true values.

All infants received vitamins A and D as a prepared concentrate in corn oil and 50 mg. of ascorbic acid daily. The mineral content of these additions was ignored, as was that of the 30 cc. of weak tea offered the infants between feedings.

Serum Analyses.—All specimens of blood were obtained by puncture from the internal jugular vein and transferred under oil to a centrifuge tube. Carbon dioxide content was determined immediately, and a correction was made for free carbon dioxide.[3] Chloride was determined by titration with mercuric nitrate[4] of a sample of serum diluted with twelfth-normal sulfuric acid. Sodium analyses were made photometrically by the uranyl zinc acetate method[5]; potassium was determined by a microphotometric cobaltinitrate method.[6] Calcium was titrated as the oxalate; phosphate and nitrogenous substances were measured photometrically by methods described by Hoffman.[7]

Urinalyses.—The chloride, phosphate and nitrogen levels were determined directly, as for serum. Calcium and sulfate were determined in a phosphate-free filtrate.[8] Because the specimens of urine were dilute, a concentrated filtrate was prepared by mixing 30 cc. of urine, 4 cc. of a 10 per cent solution of ferric chloride and 4 cc. of a 10 per cent solution of ammonium acetate and water to make 40 cc. The mixture was heated to the boiling point and filtered while hot. The content of organic sulfate as determined in trial analyses was negligible, and it was therefore ignored. Sodium and potassium were determined as for serum from a urine ash prepared in a platinum crucible by evaporation on a water bath. The last traces of water were removed in an oven, and final ashing was completed in a muffle furnace brought slowly up to 550 C.

The concentrations of organic acids were determined by the method of Van Slyke and Palmer[9] and titrable acidity was estimated by Henderson and Palmer's

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3. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 295.

4. Schales, O., and Schales, S.: J. Biol. Chem. **140**:879, 1941.

5. Hoffman, W. S., and Osgood, B.: J. Biol. Chem. **124**:347, 1938.

6. Hoffman, W. S.: J. Biol. Chem. **120**:57, 1937.

7. Hoffman, W. S.: Photelometric Clinical Chemistry, New York, William Morrow & Co., Inc., 1941.

8. Hoffman, W. S.: J. Biol. Chem. **93**:787, 1931.

9. Van Slyke, D. D., and Palmer, W. W.: J. Biol. Chem. **41**:567, 1920.

technic.[10] Ammonia was determined by aeration and titration. Creatinine was analyzed by Folin's method as adapted to the photoelectric photometer.[7] Examinations of p_H were made with a Coleman p_H meter. For the study of base economy, phosphate was expressed as milliequivalents per liter calculated on the basis of p_H 7.4.

Milk Analyses.—Chloride and nitrogen were determined directly on a specimen of the milk preparation. All other analyses were made on an ash prepared in a platinum crucible, as for urine. The final ash was dissolved in 10 per cent hydrochloric acid. For sodium and potassium analyses, aliquots of the acid filtrate were evaporated to dryness to remove the hydrochloric acid before precipitation, and the determination was similar to that for serum. For calcium analysis the solution was neutralized to p_H 5 before precipitation as the oxalate. Phosphate was determined in an aliquot diluted with 5 per cent trichloroacetic acid U. S. P.

Analyses of Stools.—The stools were collected in weighed beakers marked for 250 and 500 cc. The weight of the stools was determined by difference. When fat analyses were carried out, the stools were treated with water and thoroughly homogenized in a mortar. (A Waring type of blender was later found to be more efficient.) A weighed sample of the homogenized stool was extracted, after acidification, with ether and alcohol. The filtered extract and washings were evaporated to dryness, and the residue was extracted with petroleum benzin U. S. P. This extract was quantitatively transferred to a small weighed beaker and evaporated to constant weight. The remainder of the specimen of stool was transferred quantitatively to the original beaker and treated with 50 cc. of concentrated sulfuric acid. (When fat analyses were not carried out, the original specimens were treated directly with water and sulfuric acid.) The charred material was stirred until the solid was dissolved or homogeneously suspended. Water was added to the 250 or 500 cc. mark, and the stirring was repeated.

Chloride was estimated in an aliquot of the homogenized sample after neutralization with solid barium hydroxide, reacidification with twelfth-normal sulfuric acid and filtering. An empiric correction was made for the positive error in volume due to the precipitated barium sulfate, and for the negative error, due to the inclusion of chloride in the precipitate. The correction was estimated by the recovery analyses of known amounts of added chloride. The net error was about —5 per cent. Nitrogen was determined in an aliquot of the homogenized sample.

For the other analyses, an aliquot of the homogenized stool was wet ashed in a large Kjeldahl flask with nitric acid; then it was treated with water and reheated to remove nitrosylsulfuric acid. Phosphate was determined in an aliquot of this digest. Sodium, potassium and calcium were analyzed from an ash prepared from this digest by removal of the sulfuric acid in a platinum crucible.

BALANCE STUDIES

Table 1 gives the balances for the inorganic constituents obtained in studies on 15 premature infants on a diet of evaporated milk for three days. In addition, fat excretions in the stool are shown. A substantial gain in weight occurred in all but 3 infants (cases 13, 14 and 15). These 3 infants were 6 to 10 days old and were not yet on an adequate caloric intake. The remaining 12 babies showed not only gains in weight but also unequivocal positive balances of chloride, sodium, potassium, phosphorus and calcium, in keeping with the expected expansion of tissues and fluids.

10. Henderson, F. J., and Palmer, W. W.: J. Biol. Chem. **17**:305, 1914.

TABLE 1.—*Values for Three Day Balances for Premature Infants on a Diet of Evaporated Milk*

Case No.	Age, Days	Weight, Gm.		Chloride, Mm.	Sodium, Mm.	Potassium, Mm.	Phosphate, Mm.	Calcium, Mm.	Fat, Gm.
1	28	Start 1,860	Intake	25.5	20.0	32.3	23.5	25.2	
			Urine	18.5	17.2	16.7	14.8	0.6	
		End 1,873	Stool	0.7	0.15	7.0	2.5	15.1	14.6
			Balance	6.3	2.65	8.6	6.2	9.5	
2	37	Start 1,930	Intake	31.9	25.1	40.4	29.4	31.5	
			Urine	15.6	14.6	19.9	10.6	0.3	
		End 1,959	Stool	0.5	0.2	2.0	6.3	17.9	9.2
			Balance	15.8	10.3	18.5	12.5	13.3	
3	35	Start 2,043	Intake	31.9	25.1	40.4	29.4	31.5	
			Urine	12.1	10.5	19.9	9.0	0.2	
		End 2,128	Stool	1.2	0.3	1.6	11.0	29.9	7.0
			Balance	18.6	14.3	18.9	9.4	1.4	
4	20	Start 2,015	Intake	22.3	17.4	28.3	20.6	22.1	
			Urine	9.0	7.4	15.0	7.1	0.3	
		End 2,072	Stool	0.5	0.4	0.8	4.9	11.6	2.7
			Balance	12.8	9.6	12.5	8.6	10.2	
5	14	Start 1,959	Intake	25.5	20.0	32.3	23.5	25.2	
			Urine	9.5	7.3	13.9	7.2	1.1	
		End 2,080	Stool	0.6	0.4	1.4	3.0	8.8	2.1
			Balance	15.4	12.6	17.0	13.3	15.3	
6	16	Start 2,080	Intake	24.1	18.9	24.2	22.2	23.8	
			Urine	7.9	5.8	12.9	7.0	0.4	
		End 2,072	Stool	0.5	0.1	0.8	3.8	12.7	3.1
			Balance	15.7	12.7	10.5	11.4	10.7	
7	38	Start 1,878	Intake	25.5	20.0	32.3	23.5	25.2	
			Urine	13.6	7.0	17.2	10.2	0.4	
		End 1,922	Stool	0.5	0.3	2.2	4.2	14.9	5.2
			Balance	11.4	12.7	12.9	9.1	9.9	
8	28	Start 1,708	Intake	25.5	20.0	32.3	23.5	25.2	
			Urine	9.3	8.9	14.6	9.8	0.4	
		End 1,989	Stool	0.5	0.1	2.1	4.6	14.6	3.2
			Balance	15.7	11.0	15.6	9.1	10.2	
9	30	Start 1,724	Intake	25.5	20.0	32.3	23.5	25.2	
			Urine	13.5	10.4	7.7	11.0	0.4	
		End 1,732	Stool	0.6	0.3	4.7	1.5	8.0	10.4
			Balance	11.4	9.3	19.9	11.0	16.8	
10	14	Start 2,000	Intake	31.9	25.1	40.4	29.4	31.5	
			Urine	13.4	6.5	20.3	12.6	0.2	
		End 2,114	Stool	0.6	0.1	3.3	8.0	18.1	9.0
			Balance	17.9	18.5	16.8	8.8	13.2	
11	42	Start 2,072	Intake	35.4	27.7	44.8	32.6	35.0	
			Urine	22.7	11.9	21.7	13.7	4.4	
		End 2,228	Stool	0.9	0.2	4.9	8.4	22.9	8.2
			Balance	11.8	15.6	18.2	10.5	7.7	
12	35	Start 1,985	Intake	35.4	27.7	44.8	32.6	35.0	
			Urine	25.3	16.0	23.1	18.1	8.1	
		End 2,135	Stool	1.4	0.2	9.3	6.0	22.2	16.7
			Balance	8.7	11.5	12.4	8.5	4.7	
13	10	Start 2,106	Intake	16.0	12.5	20.2	14.7	15.8	
			Urine	11.7	10.7	9.7	6.1	0.2	
		End 2,000	Stool	0.5	0.2	1.5	2.1	6.1	1.8
			Balance	3.8	1.6	9.0	6.5	9.5	
14	6	Start 1,930	Intake	16.0	12.5	20.2	14.7	15.8	
			Urine	10.0	9.4	11.0	7.6	0.5	
		End 1,945	Stool	0.5	0.1	3.0	3.7	12.3	4.1
			Balance	5.5	3.0	6.2	3.4	3.1	
15	6	Start 1,992	Intake	16.0	12.5	20.2	14.7	15.8	
			Urine	12.7	3.2	9.7	5.5	0.1	
		End 1,837	Stool	0.5	0.1	1.1	1.3	5.9	2.9
			Balance	2.8	9.2	9.4	7.9	9.8	

The balance of chloride averaged 13.5 millimols for the 12 infants whose diet was adequate, the standard deviation being 3.8 millimols. For 8 of the 12 infants, the balance of sodium was less than that of chloride, the average balance for the 12 infants being 11.7 millimols, with a standard deviation of 3.7 millimols. The chloride content of the food mixture was also greater than that of sodium. In fact, the excess of chloride was larger than that of the balances, a finding which indicated that at least some of the excess had been excreted. For the development of new extracellular fluid of normal composition, 143 millimols of sodium would be accompanied with 115 millimols of chloride, or 11.7 millimols of sodium to 9.4 millimols of chloride. Therefore, there was in these infants an average excess of 4.1 millimols of chloride.

The stools were virtually devoid of sodium. The values for the three day period ranged between 0.1 and 0.4 millimol, the average being 0.2 millimol. Chloride was present in slightly larger quantities in the stools, the average being 0.7 millimol. The stools were semisoft and contained considerable water. It appeared, therefore, that sodium and chloride were absorbed from the intestinal lumen in concentrations greater than that of a solution isotonic with plasma.

The average positive potassium balance for the 12 infants on adequate diets was 15.2 millimols, the standard deviation being 3.5 millimols. This positive balance was in excess of what would be anticipated for the formation of new tissue. For this purpose about 3 millimols of potassium would be required for each gram of retained nitrogen. Although nitrogen balances were not determined for these infants, the study of other premature infants indicated that the positive balance of nitrogen for the three day period was about 2 Gm., and never more than 3 Gm. If these values applied here, 6 to 9 millimols of potassium was stored in excess of the quantity required to produce new tissue.

The fecal excretion of potassium was variable, and usually much higher than that of sodium or chloride. It ranged from 0.8 to 9.3 Gm. This higher and more variable content might possibly have been related to the bacterial composition of the stool.

The degree of retention of calcium and phosphorus was undoubtedly related to the content of vitamin D in the diet. Since the daily vitamin D intake varied from 200 to 800 U. S. P. units, it was difficult to evaluate the retention in this small series. Good positive balances were achieved in all 12 infants whatever the vitamin D intake. It is of interest that though the balances of calcium were of the same order of magnitude as those of phosphorus the distribution of these elements in the excreta was different. Most of the calcium was excreted in the stool; the urine contained only traces, in spite of the fact that the serum calcium concentrations usually showed high normal values. On the other hand, phosphorus was excreted principally in the urine. The fecal excretion

of phosphorus was nevertheless considerable. It was variable and seemed to bear no relation to the calcium content of the stools. Perhaps the fecal phosphorus was also related, among other things, to the bacterial composition of the stool.

Fat analyses of the stool showed variable results. The values ranged from 1.83 to 16.66 Gm. For ten additional three day balances not included in this group, the range was from 4.57 to 18.74 Gm. The average for 25 infants was 7.5 Gm. for the three day period. There appeared to be no relation between the quantity of fat lost in the stools and the gain in weight. Some of the largest losses occurred in the infants who gained the most weight during the three day period.

TABLE 2.—*Serum Electrolyte Levels in Premature Infants on a Diet of Evaporated Milk*

Case No.	Chloride, mEq./L.	Sodium, mEq./L.	Potassium, mEq./L.	Phosphate, Mg./100 Cc.	Calcium, mEq./L.	Bicarbonate, mEq./L.	Total Protein, Gm./100 Cc.
1	112	138	5.0	8.1	6.3	13.3	...
2	110	143	5.6	6.9	6.0	21.7	...
3	108	141	5.9	6.8	5.1	20.0	...
4	113	138	5.6	7.0	...	20.0	...
5	105	140	6.2	7.5	5.9	18.0	...
6	110	140	5.0	7.1	...	19.5	...
7	108	139	5.3	7.1	5.9	18.8	...
8	113	147	5.6	6.7	...	19.0	...
9	114	138	5.7	8.1	5.7	15.2	...
10	107	141	5.5	7.2	5.5	20.0	...
11	109	140	5.4	5.9	5.4	19.8	...
12	109	142	5.9	8.7	5.3	16.5	...
13	104	142	5.3	7.5	...	20.2	...
14	111	148	5.4	9.9	6.2	20.8	...
15	112	140	5.6	8.6	6.3	19.1	...
Average	110	141	5.5	7.5	5.8	18.8	...
Standard deviation	3	3	0.4	1.0	0.4	2.1	...
Average for 13 other cases	111	140	5.3	7.7	5.5	18.0	5.20

SERUM ELECTROLYTE LEVELS

Table 2 gives the serum electrolyte concentrations for the 15 subjects on whom balance studies were carried out. In addition, the average serum electrolyte levels for 13 other infants on a diet of evaporated milk are given. The range of serum chloride was 104 to 114 milliequivalents, with an average of 110 milliequivalents per liter and a standard deviation of 3 milliequivalents per liter. Only 2 infants had levels near 104 milliequivalents, which is the average for normal adults. The remaining chloride concentrations were 108 milliequivalents or higher. The average sodium concentration was 141 milliequivalents per liter, which is only slightly lower than the average of 143 milliequivalents for adults. There were no infants with levels below 138 milliequivalents, which has been regarded as the lower limit of normal for adults.[11] The standard deviation was 3 milliequivalents per liter, or only 2 per cent of the mean value.

11. Hoffman, W. S., and Osgood, B.: J. Lab. & Clin. Med. **27**:1174, 1942.

Potassium concentrations ranged from 4.7 to 6.7 milliequivalents per liter, with an average of 5.4 milliequivalents and a standard deviation of 0.4 milliequivalent. The low value for the standard deviation, which is about 7 per cent of the mean value, indicated the narrow range of serum potassium levels; yet this standard deviation was somewhat higher than that for sodium. The mean potassium level appeared to be higher than that for adults, which is probably below 5.0 milliequivalents per liter.[12] This higher average value was apparently related to the large positive potassium balances and might indicate that potassium was being retained in greater quantities than could be incorporated into new tissue.

Serum calcium and phosphate concentrations were more variable than those of chloride, sodium or potassium. The average for calcium was 5.8 milliequivalents per liter, with a standard deviation of 0.4 milliequivalent, and for phosphorus the average was 7.5 mg. per hundred cubic centimeters, with a standard deviation of 1.0 mg. The significance of these high values and their relation to the quantity of vitamin D in the diet are to be the subject of another report and will not be elaborated on here, except for the surmise that calcium and phosphate were being absorbed from the intestinal tract at a slightly faster rate than they could be utilized.

The average value for bicarbonate was 18.8 milliequivalents per liter. The values ranged from 13.3 to 23.7 milliequivalents, and the standard deviation was 2.1 milliequivalents per liter. These values were all somewhat lower than those for adults, whose average is about 27 milliequivalents per liter.[12] Thus, in terms of the adult, these premature infants on an evaporated milk diet had a slight acidosis, in keeping with the excess of serum chloride; yet they showed no clinical evidence of distress or any sign of Kussmaul breathing. As pointed out in the balance studies, there were also gains in weight and positive balance of sodium. In contrast, as will be seen in the succeeding paper,[2] in premature infants on a diet of powdered protein milk a severe acidosis developed, with a loss in weight and with bicarbonate values of about 12 milliequivalents per liter.

The sum of the average cations (if the concentration of magnesium was assumed to be 2 milliequivalents per liter) was 154 milliequivalents per liter, a value about the same as that for normal adults. The sum of the average concentrations of chloride, phosphate,[13] protein [13] and

12. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1929, vol. 1.

13. The milligrams of phosphate per hundred cubic centimeters was converted to milliequivalents per liter by multiplication by 0.57, a factor based on an assumed ratio of 3.55 to 1 for B_2HPO_4 to BH_2PO_4 at a p_H of 7.4. Protein bound by base was calculated from the formula developed empirically by Van Slyke.[12] It assumed a normal ratio of albumin to globulin.

bicarbonate was 146 milliequivalents. Thus, the difference which represents organic acid and sulfate was 8 milliequivalents per liter, a value within the range of normal for adults.[12] These observations were not in agreement with those of Branning,[14] who by difference found concentrations of organic acids of about 17 milliequivalents. The essential variation in the two groups of findings was the lower chloride levels reported by Branning.

Since infants who were given evaporated milk thrived, gained weight and grew normally, in spite of the demonstrated chloride acidosis, it was thought that the acidosis was perhaps only temporary and that eventually it would disappear. Isolated serum analyses made on infants at a later date seemed, indeed, to corroborate this surmise. For example, 7 prematurely born infants with an average age of 4 months who had been given evaporated milk continuously from the time they were brought

TABLE 3.—*Serum Chloride and Sodium Concentrations* for Premature Infants During Three Weeks of Their Stay in the Hospital*

Case No.		Date 12/1	12/4	12/7	12/10	12/13	12/16
21.....	Chloride	107	108	118	113	...	...
	Sodium	142	141	138	138	...	...
22.....	Chloride	109	111	110	108	107	...
	Sodium	139	138	139	139	139	...
23.....	Chloride	106	105	112	106	107	108
	Sodium	139	139	138	139	139	140
24.....	Chloride	117	114	110	109	108	...
	Sodium	139	141	138	140	138	...
25.....	Chloride	117	118	115	...	115	114
	Sodium	141	141	139	...	139	140
26.....	Chloride	117	117	111	110	111	109
	Sodium	141	142	142	139	139	140

* Values expressed in milliequivalents per liter.

to the premature infant station, and who were being followed in an outpatient clinic, showed chloride levels ranging from 104 to 110 milliequivalents, with an average of 107 milliequivalents. In these infants, the level of serum sodium had not changed appreciably; it ranged from 138 to 147 milliequivalents per liter with a mean of 141 milliequivalents.

In a further attempt at an evaluation of the course of the chloride acidosis, 6 infants who were on a diet of evaporated milk were followed for the last three weeks of their stay at the premature infant station by determination of their serum chloride and sodium concentrations every three days. The results are shown in table 3. The serum chloride levels tended to fall (especially in cases 24, 25 and 26), but the decline was neither rapid nor decisive in this short period. Thus, it appeared that if the serum chloride elevation did recede the fall to values found for adults was not complete until after the first few months of life.

14. Branning, W. S.: J. Clin. Investigation **21**:101, 1942.

RESULTS OF URINALYSES

Typical analyses of the cations and anions of the urine of 5 infants on evaporated milk diets are shown in table 4. A detailed discussion of the acid-base relation and of the other observations is given in the succeeding paper,[2] in which the effect of the diet of evaporated milk and that of the protein milk diet are compared. It is worth while here to point out that though the urine had a p_H between 5 and 6, as is usual for adults on an acid ash diet, there appeared to be no other stimulation for the conservation of fixed base in the excretion of acid. The ammonia nitrogen was in most instances only about 3 per cent of the total nitrogen, and its acid equivalent was less than half the titratable acidity. (In the adult, ammonia nitrogen normally represents about 5 per cent of the total nitrogen, and its milliequivalent value is higher than that of the titratable acidity.[15]) Losses of sodium and potassium in the urine

TABLE 4.—*Typical Values from Twenty-four Hour Urinalyses for 5 Premature Infants on a Diet of Evaporated Milk*

Volume of Sample, Cc.	p_H	Total Nitrogen, Gm.	Ammonia, mEq.	Nitrogen as Ammonia, %	Titratable Acidity, mEq.	Creatinine, Mg./Kg.	Organic Acid, mEq.	Inorganic Sulfate, mEq.	Phosphate, mEq.	Chloride, mEq.	Sodium, mEq.	Potassium, mEq.	Calcium, mEq.
110	5.30	704	3.26	6.5	4.08	13	3.74	1.73	4.59	7.00	4.83	6.78	0.1
125	5.30	668	3.19	6.7	6.14	16	11.9	1.87	9.58	8.91	6.65	7.73	0.1
182	5.65	728	1.61	3.1	3.74	10	3.06	1.43	4.30	7.44	5.61	8.75	0.24
230	5.21	633	1.64	3.7	3.32	14	3.86	1.27	4.08	5.82	4.97	8.82	0.08
178	5.16	605	1.21	2.8	4.40	10	3.14	1.00	4.10	5.70	4.53	6.60	0.16

were about half the intake, and this moderate excretion made possible good positive balances.

An interesting incidental observation was the excretion of creatinine, which is expressed in table 4 in the form of the creatinine coefficient (milligrams of creatinine per kilogram per twenty-four hours). The values were relatively constant from day to day and did not differ much from infant to infant. The range was from 10 to 16, which was similar to that of Marples,[16] who reported an average creatinine coefficient (if calculated as milligrams of creatinine per kilogram per twenty-four hours) of 13.7. For men the average coefficient is usually given as 23 and is believed to be related to the muscle mass of the body. The creatinine coefficients for these infants were only about 60 per cent of that of adults. However, since their relative muscle mass is also only

15. Van Slyke, D. D.; Linder, G. C.; Hiller, A.; Leiter, L., and McIntosh, J. F.: J. Clin. Investigation **2**:255, 1926.

16. Marples, E.: Creatinuria in Infancy and in Childhood: Creatinuria of Premature Infants, Am. J. Dis. Child. **64**:996 (Dec.) 1942.

about 60 per cent of that of adults,[17] the creatinine coefficients determined here could still indicate that the quantity of creatinine excreted by infants was directly proportionate to the quantity of body muscle.

COMMENT

That the newborn infant is likely to have minor disturbances in acid-base equilibrium has been recognized for some time. Marples and Lippard [18] reported a value for serum bicarbonate of 21.4 milliequivalents per liter for the infant when the diet was changed from breast milk to cow's milk. The serum chloride concentration was 108.0 milliequivalents per liter. Branning [14] reported the average level of serum bicarbonate for premature infants to be 16.8 milliequivalents per liter, but he blamed the acidosis on the accumulation of organic acids. His chloride levels were low, about 103 milliequivalents per liter. Young and associates [19] found serum chloride levels in 8 to 18 day old premature infants to be 109 milliequivalents per liter, a value similar to our own average of 110 milliequivalents. Darrow's [1] premature infants on a diet of skimmed cow's milk with "dextri-maltose" to which a small amount of sodium bicarbonate had been added showed an average serum chloride concentration of 103 milliequivalents per liter, but other infants on formulas without sodium bicarbonate had chloride concentrations as high as 114 milliequivalents per liter.

Darrow [1] suggested that the excess of chloride in cow's milk is likely to produce a chloride acidosis but offered no data to support this view. Our balance studies confirm Darrow's surmise that chloride is retained in excess of sodium, with a resultant increase in serum chloride levels and a drop in the bicarbonate levels. Our urinalyses point to a limited ability of the infant to conserve base through the increased production of ammonia. Apparently, if the stimulus is great enough, the kidneys can respond with increased production of ammonia and with a greater titratable acidity. Such a stimulus was observed in the succeeding study [2] on the effect of a diet of protein milk, in which the excess of chloride was so great that sodium was lost from the body to help in the excretion of chloride. In the case of the evaporated milk diet, sodium balances remained positive. Compensation for the excess chloride required only a moderate increase in the extracellular chloride concentration and a lowering of the bicarbonate concentration. Studies made

17. Smith, C. A.: The Physiology of the Newborn, Springfield, Ill., Charles C Thomas, Publisher, 1945, p. 196.

18. Marples, E., and Lippard, V. W.: Acid-Base Balance of New-Born Infants: Influence of Cow's Milk on Acid-Base Balance of Blood of New-Born Infants, Am. J. Dis. Child. **45**:294 (Feb.) 1933.

19. Young, W. F.; Hallum, J. L., and McCance, R. A.: Arch. Dis. Childhood **16**:243, 1941.

on the distribution of electrolytes between extracellular and intracellular compartments, as shown in the succeeding report,[2] indicated that little, if any, sodium was withdrawn from intracellular fluid during the period of the evaporated milk regimen to help in neutralizing the increased extracellular chloride.

As has been pointed out previously, the moderately increased concentration of serum chloride and the lowered bicarbonate concentrations apparently produced no disturbance in these infants. There was no demonstrable Kussmaul breathing, even though ventilation of the excess carbon dioxide might have been expected. The infants were healthy, had good cutaneous turgor and gained weight regularly. Slowly, with increased efficiency in renal function, the chloride concentration was reduced to levels nearer to that found in adults.

The slightly elevated serum potassium concentrations were probably related to the fact that the potassium balances were higher than that required for the formation of new tissue. If, as Darrow[20] maintained, the injection of potassium into the body is followed by a uniform rise of potassium concentration in both extracellular and intracellular fluids, then a high dietary retention of potassium will produce a similar effect. Furthermore, since the degree of rise in potassium concentration after an injection is determined by the rate of renal excretion, by the same reasoning, the rise in levels of serum and tissue potassium in the course of the high potassium intake during the evaporated milk diet is caused by the limitation of renal excretory function in these immature infants.

From a nutritional point of view, the diets chosen appeared to be satisfactory enough. Yet our observations impose at least theoretic objections to such a diet, in which the protein content is made high by a limited dilution of evaporated cow's milk, for the establishment of a high protein intake by such means forces at the same time a high chloride and potassium intake. Ideally, the milk should be diluted to reduce the mineral content of the diet, and a form of extra protein should be added which does not contain minerals.

SUMMARY

Electrolyte balance studies were performed for 15 premature infants ranging in age from 6 to 38 days who were on a diet of diluted evaporated cow's milk. In 12 of these infants whose diet was calorically adequate, significantly positive balances of chloride, sodium, potassium, phosphate and calcium were obtained.

The chloride balance was greater than that of sodium for 8 infants. The average chloride in excess of that required for the formation of new extracellular fluid of normal composition was 4.1 millimols.

20. Darrow, D. C.: J. Pediat. **28**:515, 1946.

The potassium balances were from 6 to 9 millimols in excess of that required for the formation of new tissue.

Serum analyses on these 15 premature infants and on 13 others showed an average chloride level of about 110 milliequivalents per liter and a bicarbonate level of about 18 milliequivalents per liter. This chloride acidosis was not accompanied with any clinical symptoms and did not interfere with growth and health. Repeated analyses showed a slow tendency for the chloride concentrations to drop to lower levels, but at 4 months of age the infants still had an average serum chloride level of 107 milliequivalents per liter.

Serum potassium concentrations were slightly higher than those for adults. These levels may be related to the high positive balances of potassium and may indicate renal retention.

The twenty-four-hour specimens showed values for p_H between 5 and 6, but there was no stimulation to increased production of ammonia or to excessive excretion of sodium or potassium. Creatinine excretion appeared to be related to muscle mass.

Though the high protein diet produced by limited dilution of evaporated milk appears satisfactory, the attending excessive retention of chloride and potassium is at least theoretically objectionable.

Dr. Philip L. Aries, attending physician (premature infants), cooperated in these studies. Miss Bess Osgood, Miss Thelma Garvin and Miss Gwenyth Stolzenburg assisted with the chemical analyses. Miss Margaret Anderson and Miss Gwendolyn Boccia assisted with the care of infants, the collection of specimens and the preparation of food mixtures.

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DEVELOPMENTAL OPACITIES OF TEETH IN A NEW ENGLAND COMMUNITY

Their Relation to Fluorine Toxicosis

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IN VIEW of the widespread interest in the use of fluorine as a prophylactic agent for the control of dental decay, a consideration of the diagnostic criteria of fluorine toxicosis becomes of unquestionable importance to the pediatrician, as well as to the dentist. There is sufficient presumptive evidence to warrant the claim that careful observation of the color and translucency of teeth may furnish the clinician valuable clues regarding the health history of the child. Enamel tissue frequently furnishes physical signs of past or present disturbances of general metabolism. The present paper deals with some of the difficulties that arise when certain opaque hypoplasias of this tissue are looked on as physical signs of fluorine toxicosis.

Enamel tissue is ordinarily devoid of macroscopically detectable coloring material. In this respect it differs from the underlying dentinal tissue, which reflects to a degree the circulatory condition of the dental pulp and of the entire organism. When there is no interference with the hydration of tooth enamel, its translucency is entirely dependent on the physical organization of its chemical constituents. It is evident, therefore, that little real advance in the utilization of teeth for diagnostic purposes is possible until the physician and the dentist know more about the factors which govern the physical characteristics of this tissue.

Opaque enamel never has been the subject of exhaustive, methodical investigation. No satisfactory studies of the prevalence of the clinical varieties of opaque enamel have been published. As matters stand today, most textbook writers recognize two clinical types of the imperfection, although they do not draw clear lines of differentiation between them.

From the Forsyth Dental Infirmary for Children.

The Dental Study Unit, Yale University School of Medicine and the United States Children's Bureau gave assistance in the collection of the original data used in this study. The analysis of the data was made by the author. Permission to utilize these data was obtained from Dr. Ethel C. Dunham, Consultant in Pediatrics at the Children's Bureau of the United States Department of Labor, Washington, D. C., and from Prof. B. G. Anderson, director of the Dental Study Unit at the Yale University School of Medicine.

SURVEY OF LITERATURE

As far back as 1842, Linderer and Linderer [1] included a description of "flecks in the enamel" in the second edition of their "Handbuch der Zahnheilkunde." They referred quite obviously to what was later known as "white spots" in the enamel—maculae albae substantiae vitreae dentis.

The second clinical variety of opaque enamel has acquired several names, the most popular of which is "mottled enamel." Credit for the earliest description of the second variety of opaqueness has been given to Stefano delle Chiaie, of Naples,[2] who contributed extensively to medical and biologic literature during the first half of the nineteenth century. The first American reference to the condition was by Eager,[3] in 1901, but the papers that really familiarized members of the dental profession with the subject appeared fourteen and fifteen years later, after Rodriguez [4] and McKay and Black [5] reported on their studies of teeth with "Colorado brown stain" in the United States and after Gasparrini and Piergili [6] published an article on the etiologic aspects and treatment of "denti scritti" in Italy.

Aside from innumerable reports on so-called mottled enamel, there seem to exist no satisfactory studies on the incidence of dentitions with opaque enamel. Almost all available literature refers to the prevalence of "mottling" in certain regions of endemic fluorosis, particularly in the central and southwestern sections of the United States.

As for the relative frequencies of "mottling" of the various classes of teeth, nothing definite seems to have been recorded regarding the teeth of Caucasians living in the United States, except for a brief remark by McKay,[7] who stated in 1929: "It is extremely rare to find the bicuspids or molars with damage that even approaches that of the incis-

1. Linderer, C. J., and Linderer, J.: Handbuch der Zahnheilkunde, ed. 2, Berlin, Schlesinger, 1842, vol. 1, p. 124.

2. delle Chiaie, S., cited by Eager.[3]

3. Eager, J. M.: Denti di Chiaie (Chiaie Teeth), Pub. Health Rep. **16**:2576, 1901.

4. Rodriguez, F. E.: The United States Indian Service Field Dental Corps: A New Field of Activity in Which Physician, Dentist and Teacher Collaborate, Tr. Panama Pacific Dent. Cong. **1**:291, 1915.

5. McKay, F. S., and Black, G. V.: A Brief Synopsis of a Paper Entitled Mottled Teeth: An Endemic Developmental Imperfection of the Enamel of the Teeth Heretofore Unknown in the Literature of Dentistry, Tr. Panama Pacific Dent. Cong. **1**:25, 1915; An Investigation of Mottled Teeth: An Endemic Developmental Imperfection of the Enamel of the Teeth, Heretofore Unknown in the Literature of Dentistry, Dent. Cosmos **58**:477, 627, 781 and 894, 1916.

6. Gasparrini, O., and Piergili, B.: Azione decalcificante de alcune acque potabili sopra lo smalto dei denti nel periodo della dentizione, Ann. de chim. applicata **5**:93, 1916; abstracted, Chem. Abstr. **10**:1648, 1916.

7. McKay, F. S.: The Establishment of a Definite Relation Between Enamel That Is Defective in Its Structure, as Mottled Enamel, and the Liability to Decay (II), Dent. Cosmos **71**:747, 1929.

ors." The data presented by Dick[8] on children examined in a "non-endemic" area (London) seem to bear out this statement, while those cited by King[9] on children studied in an "endemic" area (Maldon, England) do not. The statements made by Day[10] on the distribution of opaqueness in the teeth of Indian children likewise contradict the comment made by McKay.

Although Arnim, Aberle and Pitney[11] observed numerous opaque spots in the enamel of the permanent teeth of 204 Pueblo Indian children, aged 7 to 11 years, in an area of endemic fluorosis in New Mexico and Arizona, the incomplete presentation of their statistical findings makes it impossible to determine with any degree of certainty what classes of teeth were most frequently affected.

One of the most interesting contributions to the literature dealing with clinical aspects of opaque enamel was that by Sognnaes,[12] who studied dental conditions in Tristan da Cunha in 1937 and 1938. It is reasonably clear from his account of the clinical criteria employed that the "white spots" seen in the teeth of the islanders may be comparable, so far as appearances are concerned, to the "discrete developmental opacities" discussed in the present report. With the exclusion of the third molars, 16.1 per cent of the permanent teeth of the islanders examined were "spotted." The opaque defects were observed oftenest in the incisors and canine teeth of the maxillary arch.

Sognnaes was not ready to state that the hypoplastic[12a] defects seen by him in Tristan da Cunha were due to mild fluorine toxicosis, even though this possibility could not be ruled out definitely. His and Armstrong's report[13] on the chemical composition of the islanders' teeth strongly suggested that the fluorine content of these teeth was higher than that of sound teeth obtained from a low fluorine region (Minnesota) in the United States.[14] Finally, if one should review carefully the data

8. Dick, J. L.: Abnormal Conditions of Enamel in Cases of Malnutrition, Lancet **2**:456, 1918.

9. King, J. D.: Mottled Enamel, M-Hypoplasia and Dental Caries, Dent. Rec. **64**:102, 1944.

10. Day, C. D. M.: Chronic Endemic Fluorosis in Northern India, Brit. Dent. J. **68**:409, 1940.

11. Arnim, S. S.; Aberle, S. D., and Pitney, E. H.: A Study of the Dental Changes in a Group of Pueblo Indian Children, J. Am. Dent. A. **24**:478, 1937.

12. Sognnaes, R. F.: A Condition Suggestive of Threshold Dental Fluorosis Observed in Tristan da Cunha: I. Clinical Condition of the Teeth, J. Dent. Research **20**:303, 1941.

12a. The author prefers the term "hypoplasic" to the more usual "hypoplastic."

13. Sognnaes, R. F., and Armstrong, W. D.: A Condition Suggestive of Threshold Dental Fluorosis Observed in Tristan da Cunha: II. Fluorine Content of the Teeth, J. Dent. Research **20**:315, 1941.

14. Armstrong, W. D., and Brekhus, P. J.: Possible Relationship Between Fluorine Content of Enamel and Resistance to Dental Caries, J. Dent. Research **17**:393, 1938.

published by Armstrong and associates [15] in 1938 and 1941, one would find that the chemical analyses presented are definitely suggestive of a correlation between the fluorine content of the enamel and the morphologic classification of the individual teeth.

The surveys by Spira [16] in England are of special interest, since they indicate that opaque hypoplasias of tooth enamel are not necessarily confined to regions of endemic fluorosis. Similar studies of other population groups living in areas with a fluorine content of less than 0.25 part per million in the public water supplies have not come to my attention.

The observations recorded by Anderson [17] on developmental defects in the enamel are worthy of mention. Although this investigator saw much "mottled enamel" of the classic variety in China, he wrote that "differentiation of the various types of opaque enamel . . . is often difficult."

MOTTLED ENAMEL

The association of the term "mottled enamel" with fluorine toxicosis is too well known today to require elaboration in this connection. Yet, despite the vast amount of literature that has been written on "mottled enamel," I was unable to locate even one satisfactory description stating precisely what is meant by the term, which was coined by Black in 1915. "Mottled," which is derived from the same root as "motley," signifies something "marked with spots of different colors," "dappled" or "spotted," according to Webster's "New International Dictionary." A large percentage of the teeth with opaque enamel are not "marked with spots of different colors," any more than they are "dappled" or "spotted." In spite of this, numerous investigators have employed the term as a synonym for any form of opaque enamel seen in the clinic, without demanding that it be subjected to a critical evaluation before it is accepted as a part of the scientific terminology of the clinical pathologist.

According to Dean,[18] Gordon,[19] Moulton [20] and other recent writers, "mottled enamel" is any enamel that is essentially normal in form and contour, but that exhibits some diminution in translucency which may

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15. Sognnaes and Armstrong.[13] Armstrong and Brekhus.[14]

16. Spira, L.: Incidence of Mottled Teeth, Lancet **1**:649, 1942; Endemic Fluorosis in Great Britain, Edinburgh M. J. **50**:237, 1943.

17. Anderson, B. G.: Developmental Enamel Defects: Clinical Descriptions and Classification, Am. J. Dis. Child. **63**:154 (Jan.) 1942.

18. (*a*) Dean, H. T.: Classification of Mottled Enamel Diagnosis, J. Am. Dent. A. **21**:1421, 1934. (*b*) Dean, H. T., and Arnold, F. A.: Endemic Dental Fluorosis or Mottled Enamel, ibid. **30**:1278, 1943.

19. Gordon, S. M.: Dental Science and Dental Art, Philadelphia, Lea & Febiger, 1938, p. 387.

20. Moulton, F. R.: Fluorine and Dental Health, Publication 19, American Association for the Advancement of Science, Lancaster, Pa., Science Press Printing Company, 1942.

or may not be associated with loss of surface glaze, irregular pitting and simple or variegated pigmentation. It is evident that the term as used by many investigators covers all varieties of opaque enamel and includes all gradations of the imperfection from tiny, discrete flecks to instances of diffuse opaqueness involving entire crowns.

The typical "mottled" defect described by McKay and Black [5] and other early writers was not a readily delineated, or discrete, lesion. According to them, the defective areas in the enamel of a given tooth were not in clearcut contrast with the surrounding sound tissue of the same tooth. The pigmentation present in the defects was stated to appear posteruptively, as a rule, and then increase with age, especially in the tooth surfaces that were exposed to light when the lips were parted. The statements of the early investigators never led one to consider the question whether most deciduous dentitions should be classified as "mottled," since their enamel covering is almost invariably whiter and more opaque than that of the permanent dentitions. This possibility is not excluded by the vague definitions of "mottled enamel" given by many writers today. The aforementioned weakness in the current definitions of the term is of special interest in view of the fact that most investigators have repeatedly recorded their observation of the infrequent mottling of deciduous teeth.

The indistinctly delineated character of classic "mottling" which has no secondary discoloration makes it almost impossible to secure satisfactory photographic reproductions of the defect. For this reason, no illustrations of "mottled enamel" accompany the present article.

WHITE SPOTS

The earliest descriptions of "mottled enamel" did not include the defects in the teeth frequently termed "white spots." According to numerous published descriptions, these opaque defects are developmental in origin; I myself have seen many of them in teeth removed before eruption. A clinic such as the Forsyth Dental Infirmary affords one many opportunities for observing the existence of these "spots" in teeth that are just emerging through the gingiva. The purely developmental origin of classic mottling is not quite so clear, however. Beust,[21] for instance, stated that it was produced after eruption, while the observations recently recorded by Weaver [22] in England lead one to regard the etiology of mottling ("dental fluorosis") as still unsettled. As a rule, the "mottled" defect becomes more pronounced as the person ages, while the reverse can be said of the "white spot." This statement is

21. Beust, T. B.: A Contribution to the Etiology of Mottled Enamel, J. Am. Dent. A. **12**:1059, 1925.

22. Weaver, R.: Fluorine and Dental Caries: Further Investigations on Tyneside and in Sunderland, Brit. Dent. J. **77**:185, 1944.

not intended to convey the implication that certain developmental deviations are not necessary for the clinically observed defects seen in "mottled" teeth. It is wholly possible that the pathogenesis of mottling is both preeruptive and posteruptive in time, while that of the "white spot" is entirely preeruptive.

The defects known as "white spots" are discrete opaque areas in the enamel which, unless pigmented, appear white or ashy gray, in definite

Fig. 1.—The upper photograph shows an extracted right first incisor from the maxillary arch with a distinct cloudlike, opaque area in the vestibular surface (× 6½). The lower part shows discrete developmental opacities in the teeth of a white man, aged 22. (The picture was taken with a red filter to accentuate the contrast with unaffected enamel.)

contrast to the surrounding translucent tissue. They are usually small, with an irregular, rounded, cloudlike shape, and they seldom involve more than a fraction of the total area of a crown surface (fig. 1). The smaller opacities appear to be covered with the same dense, smooth-appearing material as the rest of the enamel, but the larger ones may lack the glazed surface in the central portion. In such cases it is rela-

tively easy to press the point of a sharp instrument into the soft, chalk-like tissue in the center of the opaque area. The small opacities, which are met with frequently, are seldom pigmented, whereas the large ones, which are much less common, are often discolored yellow, brown or orange. The discoloration is present at the time the tooth erupts. It may be distributed evenly, but in the majority of cases it is most intense near the center of the defective area. If a tooth with an opaque "spot" in the enamel is placed in an acid solution for a few hours, it will be observed that the imperfect tissue corrodes more rapidly than the sound tissue.

RECENT INVESTIGATION

Clinical Material.—In order to obtain definite information about the occurrence of opaque enamel in the permanent teeth of persons born and reared in a "non-endemic" New England community, 170 dental records which I completed in 1939 and 1940 were analyzed. The persons furnishing this clinical material were examined in New Haven, Conn. One hundred and ten of the aforementioned persons had been given a complete dental examination by me in conjunction with a medical research project conducted by the United States Children's Bureau. Another group examined consisted of 40 persons seen in the New Haven Hospital. The majority of them were patients who came to the outpatient dental clinic for the removal of teeth. The remaining 20 persons were patients who had a history of rheumatic heart disease and were being studied at the hospital for sequelae of this disease.

The range in age for the entire group was from 13.21 to 30.39 years, except for 3 somewhat older persons. The mean age of the 89 men and the 81 women examined was 17.35 years. Almost all of them were natives of Connecticut, although the racial backgrounds differed widely.

In all examinations special attention was given to the various forms of distinctly contrasting opacities in the enamel. No attempt was made to record faithfully and accurately the frequently observed instances of indistinctly delineated diffuse opacities, which were in such poor contrast to the adjacent enamel tissue that it was exceedingly difficult to decide how much of the enamel crown or how many of the individual teeth were affected. Careful attention was paid to the discrete, rounded opacities popularly known as "white spots" and to the instances of opaqueness of the entire crown in which the teeth involved were in distinct contrast to the more translucent members of the dentition.

Little attention was paid to opacities in the approximal (or contact) surfaces of the teeth on account of the impossibility of inspecting all these surfaces in every dentition examined. Defects of the third molars were treated in the same manner, as the number of erupted third molars seen was too small to be of much statistical value. However, although all imperfections of approximal surfaces and of third molars are disregarded in the detailed analyses which follow, they were recorded whenever it was possible to do so without undue difficulty.

Gross Observations.—The great prevalence of opaque hypoplasias in the teeth of persons living in a community with little or no fluorine in its water supply is revealed by the discovery of one or more teeth with distinct "white spots" in the enamel in 142, or 83.5 per cent, of the 170 persons examined. Only the nonapproximal surfaces of the teeth were considered in computing this percentage. No "mottled enamel" of the undisputed variety was encountered. Many of the per-

sons lacked one or more permanent teeth which had been lost on account of dental decay (necrotic odontoclasia). Most of the missing teeth belonged to anatomic groups which exhibit high frequencies of developmental abnormalities of enamel tissue. The percentages given in the tabulation summarize the character of the clinical material studied.

	Per Cent of Dentitions
Distinct opacities in one or more nonapproximal surfaces, not counting the third molars	83.5
Distinct opacities in third molars only	1.8
Distinct opacities in approximal surfaces only, in any teeth	1.8
Only diffuse, though recognizable, opaqueness in one or more teeth	3.5
Indeterminable	9.4
Total	100.0

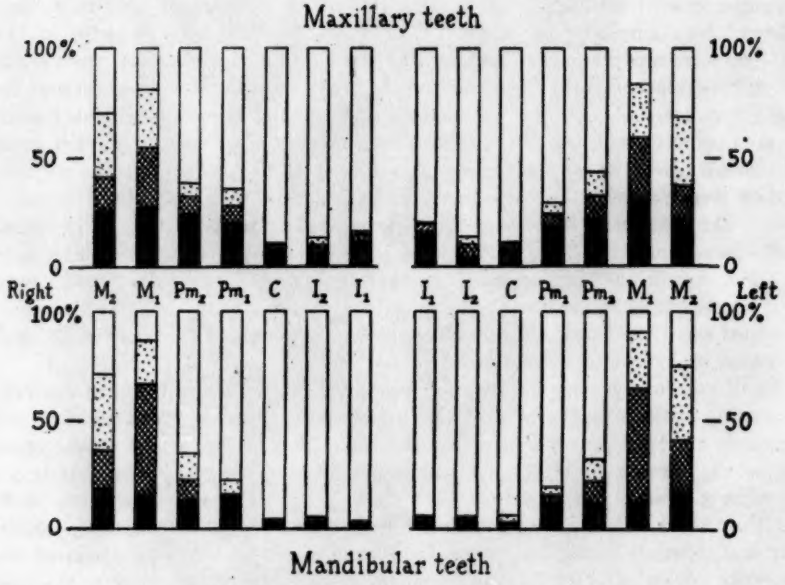

Fig. 2.—Graph showing the results of a gross survey of the total sample of 170 dentitions. The solid white portions of the bars represent the percentage of all teeth definitely not showing opaque enamel. The dotted white portions show the percentage of all teeth in which the opacities were not appreciably obscured by lesions or fillings. The hachured portions show the percentage of dentitions in which many teeth probably showed opaque enamel, and the solid black portions represent the percentage of teeth which definitely showed opacities.

The results of a gross survey of the total sample of 170 dentitions are shown graphically in figure 2. The observations on 55 Negroes were not separated from those for 115 Caucasians in calculating the percentages. The solid black portions of the bars represent the percentages for the teeth which revealed some opaque enamel regardless of the amount of enamel left for study. Although many teeth were either decayed or filled, the remaining portions of their crowns had obvious

opacities; therefore, all such teeth could be designated as definitely positive for opaque enamel. The solid white portions of the bars indicate the percentages of intact sound teeth without any opaque enamel. These teeth could be designated as definitely negative for this defect. The remaining teeth were classified as probably negative for opaqueness if there were no grounds for the belief that a small lesion or filling in the tooth obscured the picture appreciably. All other teeth were designated as partially positive for the structural imperfection.

The collective distribution pattern of the discrete developmental opacities of the "white spot" type in the enamel of the 170 permanent dentitions examined bears a strong resemblance to the collective distribution pattern of lesions which has been recorded repeatedly in studies

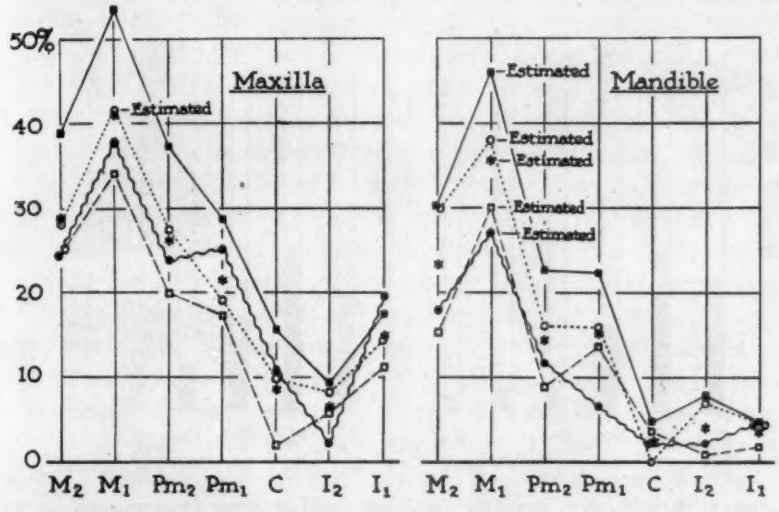

Fig. 3.—Graph showing percentage of teeth with opaque spots in relation to race and sex. Asterisks indicate the percentage for the sample group (170 persons) as a whole. Solid black squares indicate the percentages for 32 Negro boys and clear squares indicate the percentages for 57 white boys; solid black circles show the percentages for 23 Negro girls, while the clear circles indicate data on 58 white girls.

of dental decay. Not only are the opacities distributed fairly symmetrically in the two halves of each arch, but the maximum frequencies seem to occur in the first molar teeth and the minima occur definitely in the incisors and canines of the mandible. The lowest frequencies in the maxilla are for the canines and the second incisors.

In order to verify these observations with more dependable data, 73 records were singled out from the original series of 170 in such a manner that a minimum number of cases with uncertain (i.e., "partially positive") data were included. This select statistical material consisted of the records of 42 white and 31 Negro persons. A survey of these records confirmed fully the results obtained for the total material.

Influence of Race and Sex.—Since the first two analyses were made on racially mixed clinical material, it was of interest to compare data on Caucasians with similar data on Negroes. The series of 73 records mentioned previously was divided, therefore, into two parts on the basis of race. An analysis of these data showed clearly that there is no striking difference in the frequencies of opaque enamel in the two racial groups. The averages for the maxillary teeth are definitely higher than those for the mandibular teeth in both groups, although the contrast between the two jaws is stronger in the Negroes than in the Caucasians. Because of the limited amount of clinical material analyzed, the latter observation may have no special significance.

The results of a further analysis of the available material from the standpoint of sex are summarized in the graph in figure 3 and require

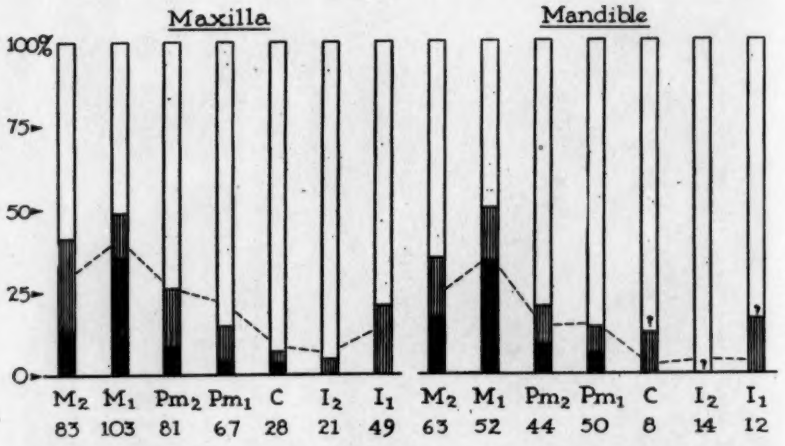

Fig. 4.—Combination line graph and bar chart showing frequency of the three main forms of opacities of enamel in relation to classes of teeth. Numbers appearing below the chart indicate the number of "spotted" teeth studied in each morphologic class. The broken line shows the frequency of teeth with any form of discrete opacity in the enamel in the total sample. The solid black portion of a bar indicates the percentage of teeth with the entire crown distinctly opaque; the portion with vertical lines denotes the percentage with two or more separate spots, and the clear portion the teeth with only a single macroscopic spot.

little comment. The Negro boys examined in New Haven had on the average much more opaque enamel than the Negro girls. In the case of the white persons, the relative frequencies were definitely higher for the teeth of girls than for those of boys.

Details of Distribution Pattern.—The composite line graph and bar chart shown in figure 4 presents the results obtained by analyzing the records for the three main varieties of distinctly contrasting opaque enamel encountered. The lone "spot" was the commonest form of the abnormality in the teeth examined. Although a large number of the first and second molars were seen to be hypoplastic, the relative number

of single discrete opacities in these teeth was definitely less than in any of the other permanent teeth. The 14 mandibular second incisors with imperfect enamel had no other form of opacity. It is realized, however, that the percentages for the mandibular incisors and canines are undependable on account of the small quantity of data on these teeth. Multiple "spotting" was most frequent in all the first and second molars, the maxillary second premolars and first incisors and the mandibular first incisors. The occurrence of more than two opaque areas in a single tooth was relatively infrequent.

One of the most surprising results of the investigation was that relating to the optical quality of the enamel covering of the first molars. As is shown in figure 4, the entire crown of a large percentage of these teeth was distinctly opaque, so that a careful study of many dentitions revealed them in unmistakable contrast with the more translucent adjoining teeth. At first, it was suspected that this generalized opacity of the crown might have been due to the frequent presence of lesions or fillings in these teeth, but repeated examinations of sound and necrotic teeth soon convinced the examiner of the incorrectness of such an explanation. No incisor was encountered in which the entire crown was distinctly opaque. This form of opaqueness was confined rather clearly to the molars and premolars, although a few maxillary canines also revealed it.

There is a clear parallelism between the frequencies of opaqueness in the different classes of teeth and the extent of the opaque areas in the individual teeth. In others words, not only are the molars afflicted more frequently than any of the other teeth, but they also tend to be marked more extensively than the other teeth. The mandibular incisors and canines, together with the maxillary second incisors, show the least degrees of easily observable involvement. It is hardly necessary to point out that even were an exactly computed allowance made for the differences in the surface areas of the visible portions of the various crowns, the molars would still be found to have appreciably higher relative frequencies of opaque enamel than the incisors and canines in either jaw.

Pigmentation and Rickets.—Seventy, that is, 10.4 per cent, of the 675 teeth with some distinct opaqueness had definite coloring of the defective enamel. The coloring was invariably yellow, brown or orange, or some blend of these three. Only 1 tooth had two differently colored opaque areas: a yellow "spot" in the vestibular surface and a brown one in the lingual surface. In only 3 dentitions was it possible to find opacities of two unlike colors, although, with the 1 exception mentioned previously, the colors were always in different teeth. If these 3 dentitions are excluded, it is difficult to speak of any true "mottling" of the enamel in any of the permanent dentitions examined.

Of the 70 teeth with pigmented opacities, 88.6 per cent belonged to persons who had roentgenographic evidence of either definite or ques-

tionable rachitic stigmas in their pelvic bones or dental evidence of spasmophilic episodes during the development of their permanent teeth. Zonal aplasia of the enamel, which is also known as gross hypoplasia of this tissue, is frequently associated with rickets. No detailed analysis of the observations related to the association between opaque enamel and rickets will be attempted in this paper. It is sufficient to note that the two clinical types of defective enamel appear to have different etiologic mechanisms.

COMMENT

This report deals with hypoplasias of dental enamel that ordinarily were not listed under the term "mottled enamel" prior to 1934, when Dean [18a] published his well known classification of various degrees of "mottling." The clinical material studied in New Haven, Conn., contained no examples of the classic "mottled" defects described in the earliest papers on the subject. The data were gathered in a geographic

*Frequencies of Discrete Opacities in the Permanent Teeth of 188 Persons Examined in Tristan da Cu and of 170 Examined in New Haven, Conn.**

Morphologic Class	Maxilla								Mandible							
	M3	M2	M1	Pm2	Pm1	C	I2	I1	M3	M2	M1	Pm2	Pm1	C	I2	I
Tristan da Cunha: Teeth with "white spots"	8.2	11.3	14.8	15.6	21.8	23.8	20.6	35.2	23.2	14.0	16.6	11.4	13.0	11.9	7.9	7
New Haven, Conn.: Teeth with discrete opacities involving only part of the crown	—	25.4	27.9	23.9	20.4	8.1	6.5	14.8	—	20.0	20.8	13.0	14.1	2.4	4.1	1
New Haven, Conn.: Teeth with distinctly contrasting opacities of any type	—	28.8	41.0	26.1	21.4	8.4	6.5	14.8	—	23.3	30.1	14.3	15.0	2.4	4.1	1

* Data are expressed as percentages.

region that has less than an appreciable amount of fluorine (less than 0.25 part per million) in the public water supplies. These data are of particular interest in view of the current belief that opaque defects of enamel are of common occurrence only in regions of endemic fluorosis. The discovery of distinct developmental opacities in 87 per cent of the permanent dentitions examined in New Haven is an unexpected finding, which leads one to suspect that careful surveys of other population groups in New England might reveal a similar prevalence of these defects in the permanent dentition.

Exclusive of the third molars, the mean frequency of teeth with "white spots" in Tristan da Cunha was 16.1 per cent, which is only slightly more than the average of 14.6 per cent for "spotted" teeth in New Haven. The high percentage of such defects in New Haven was obtained in spite of the large number of missing and unerupted teeth in the sample of population.

A study of the table reveals some remarkable contrasts between the patterns of distribution of "white spots" in the two widely separated localities just mentioned. In Tristan da Cunha the maxillas showed a concentration of opaque defects in the ventral segments of the arch,

but in New Haven most of the defects were in the dorsal segments of the arch. Even if one should disregard the uniformly opaque enamel crowns seen in Connecticut, one would still find the first and second molars of the maxillary arch to be the most frequently affected teeth. The incisors and canines of the Tristanites were from two and one-half to three times as frequently "spotted" as those of the New Haven series. Although the contrasts between individual teeth are much less striking in the mandible, the molars were definitely less often affected in Tristan da Cunha than in New Haven, while the incisors of the islanders were twice as often opaque as were those of the city dwellers in New Haven. The discrepancy between the figures of each group for the mandibular canine is even more noticeable.

The fluorine content of the water used for drinking and cooking in Tristan da Cunha is reported to be only 0.20 part per million, which is well below the concentration that is considered virtually nonproductive of opaque enamel. According to a statement received in response to an inquiry sent to the city water company early in 1946, the fluorine content of the water supplies of New Haven is considered of zero magnitude. The concentration of fluorides is known to be generally low in the adjoining states of Massachusetts [23] and Rhode Island,[24] which are geologically and climatically similar to Connecticut. The average concentration in the water supplies of these two states is 0.20 part per million. The public water supplies of the city of Newburgh, N. Y., some 25 miles (40 kilometers) west of the Connecticut border, contain only 0.12 part of fluoride per million.[25] In view of these facts it is safe to infer that if the New Haven water contains any fluoride at all the concentration is even less than that of the natural spring water in Tristan da Cunha. It cannot be argued that the persons in New Haven obtain more of this halogen from seafoods than do the Tristanites, for whom saltwater fish is an obligatory item in the daily diet.

By utilizing the figures published by Arnim and associates [11] for children examined in an area of endemic fluorosis in the United States, the following frequencies for teeth with "white spots" can be derived:

	Per Cent
First molars	25.4
Second incisors	19.8
First incisors	28.4

It is not possible to calculate the values for the maxillary and mandibular teeth separately from the data furnished.

23. Special Report of the Department of Public Health Relative to the Decay of Teeth Resulting from a Lack of Fluorine, Commonwealth of Massachusetts (House, no. 1608), December 1945.

24. Parks, W. G.; Robinson, M., and Law, M.: Fluorides in the Natural Waters of Rhode Island, J. Am. Water Works A. **28**:1064, 1936.

25. Fluorine Experiment in Newburgh, N. Y., New York State Department of Health, Illinois Dent. J. **13**:509, 1944.

The data by Sognnaes, Arnim and many others are clearly out of harmony with those obtained from the New Haven survey. It still remains to be shown that fluorine is ever directly responsible for the hypoplasia evidenced in the production of opaque enamel. The fact that fluorine has been present commonly in the same areas as the "mottled enamel" defect certainly cannot be accepted as proving that it is responsible for the discrete developmental opacities discussed in this report.

The gradual disappearance of opaque areas in the enamel as the teeth mature cannot be explained on the basis of the fluorine content of dental tissues. The clinical observation just cited was made in regions free of fluorides, as well as in those with a low fluoride content in food and water supplies. No one has yet shown that the fluorine content of the teeth definitely increases as a person grows older. Aside from this gradual disappearance with age, there is nothing to suggest that the general translucency of normal enamel diminishes to such an extent as to remove completely the contrast between the dead-white opaque areas and the rest of the tissue. What diminution in translucency does take place as a person ages can hardly be credited to one chemical element.

It is quite evident that failure to place the study of opaque enamel defects on a well defined descriptive basis has led to much confusion. The evidence presented in this paper favors the view that the original tendency to differentiate between "mottled" defects and other qualitative defects (such as "white spots") of tooth enamel is preferable to the recently introduced custom of placing all such hypoplasias in the same descriptive and etiologic category. Indiscriminate use of the diagnostic term "chronic dental fluorosis" as a substitute for the older descriptive terms certainly is not justified today.

If it can be established that there is a consistent association between the prevalence of the diffuse opaque defects termed "mottling" by the early writers and the fluorine content of the individual teeth, then the possibility remains that the distribution pattern of such defects is not identical with that due to other etiologic agents. The pattern of the defects seen in New Haven is not suggestive of "chronic dental fluorosis" or of "mottling." The difference in the clinical patterns is evident not only in the distribution of the defects in the dental arches but also in the form of the defective areas in the individual teeth.

Better understanding of the diagnostic significance of "white spots" becomes an urgent necessity today in view of the large-scale experiments with fluorinating certain public water supplies. If these defects of enamel tissue are not reliable signs of "chronic dental fluorosis," as has been intimated by several authorities, then it is obvious that such an interpretation in gathering statistical data on fluorine toxicosis is fraught with possible danger.

The posteruptive behavior of qualitative defects of enamel tissue has been largely ignored. However, in view of the nonstatic character of many opacities in the teeth, it would seem dangerous to proceed on the assumption that the metabolic activities of the dental pulp need not be considered in all attempts to evaluate the diagnostic significance of the defects discussed in this paper. This conclusion is strengthened by the data which indicate a linkage between the health status and the nutritional history of the individual person and the clinical appearance of his teeth.

CONCLUSIONS

Opaque defects of the "white spot" type in the permanent teeth are not reliable signs of "chronic dental fluorosis." There is an acute need for a reconsideration of the classification of enamel hypoplasias. Murray and Wilson [26] stated that it is "evident that a further consideration of the grading of fluorosis is required" in examining teeth. This remark by two investigators outside the dental profession is of considerable interest in view of my own conclusions. Experimental study of the physiology of the dental pulp is needed before the diagnostic significance of opacities of the teeth can be fully understood.

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26. Murray, M. M., and Wilson, D. C.: Fluorosis and Nutrition in Morocco: Dental Studies in Relation to Environment, Brit. Dent. J. **84**:97, 1948.

Case Reports

DEATH OF A NEWBORN INFANT FROM INTRATRACHEAL INSUFFLATION

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RESUSCITATION of the newborn infant is one of the major problems in the delivery room. The specific mode of treatment is still a controversial issue, and each clinic has its own routine to care for the emergency of neonatal asphyxia. The use of positive air pressure for expansion of the lungs is a practice which dates back to the first use of mouth to mouth breathing, and it has since been refined by the introduction of mechanical devices which control the pressure of the air inflow. The danger of overinflation of the lung is one which is not to be ignored, and in the opinion of some authors it should be a procedure only of last resort.[1]

The following is a report of a case in which the use of positive pressure insufflation resulted in a fatal outcome. The mechanism involved is reviewed.

REPORT OF CASE

A premature baby boy of thirty-six weeks' gestation, weighing 2,900 Gm., was born by normal spontaneous delivery and was lethargic after birth. After the pharynx was cleared, he managed to take a few shallow gasps, but his condition was considered asphyxia pallida and further measures were deemed necessary. The mother had been given 100 mg. of meperidine hydrochloride N.N.R. ("demerol") and 1/150 grain (0.4 mg.) of scopolamine hydrobromide U.S.P. two hours before delivery. The baby was examined laryngoscopically, and an intratracheal catheter was introduced under direct vision. After suction of the trachea, the catheter was connected directly to the oxygen outflow of a Kreiselman Moxel-Heidbrink resuscitator which was set to flow at 7 liters per minute. Almost instantly after the oxygen flow was started the baby was noticed to stiffen; the abdomen become distended, and subcutaneous emphysema was noted. The heart beat stopped, and the baby was pronounced dead.

The clinical explanation for the abdominal distention was the possibility that the catheter had by error been introduced into the esophagus. The clinical diagnosis was ruptured viscus in the abdomen.

Postmortem Examination.—Autopsy revealed the body of a premature baby boy which weighed 2,900 Gm. and measured 29 cm. from crown to rump and 43 cm. from crown to heel. The occipitofrontal circumference was 29.5 cm. The body

From the Department of Pathology, Queens General Hospital and Triboro Hospital.

1. Grulee, C. G., and Sanford, H. N., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 1, chap. 42.

was well formed and covered by a fine layer of lanugo hair, with black hair over the scalp. The finger nails covered the ends of the fingers, and the umbilical cord was well tied and its surface shiny and glistening. The abdomen was flat and soft. The abdominal cavity contained 50 cc. of straw-colored fluid. No hiss of air was noted to escape on opening the abdomen. The pleural cavities were opened under water. From the right pleural cavity air bubbles were seen to rise to the surface when the parietal pleura was nicked. On lifting the right lung and looking through the transparent visceral pleura, a pocket of air was seen trapped above the pleural dome, between it and the deep cervical tissues. The azygos and hemiazygos veins were noted to be distended to an unusual degree. Through the mediastinal pleura air was seen in the posterior mediastinum.

The right lung was unusually bright red and crepitant throughout. An azygos lobe was present. Under the visceral pleura small blebs of air, about ten in number and measuring 1 to 2 mm. in diameter, were noted. One larger bleb on the diaphragmatic border of the lower lobe was 5 mm. in diameter. All these blebs were found intact. The lungs were removed within a block and placed under water. A catheter was introduced into the trachea. With only minimal air pressure from mouth blowing, air bubbles were seen to escape from a perforation in the hilus of the right lung. The left lung showed congenital atelectasis, being deep blue-red, firm and noncrepitant. There was a pinkish tint at the mediastinal border of the lower lobe as evidence of some aeration. The trachea and bronchi were clear. The lungs together weighed 50 gm.

The pericardial cavity was seen to contain air bubbles with only minimal fluid present. The heart weighed 8 Gm. The cardiac muscle was not thickened, and its chambers and valves and the endocardium were entirely natural. The foramen ovale and ductus arteriosus were widely patent. The coronary sinus and the ostiums of the coronary arteries were patent.

The thymus covered most of the pericardial surface. No air was noted in this region. The thoracic portion was light brown. The cervical portion was bluish, and many petechial hemorrhages were noted on its surface. The brain showed moderate congestion and edema. The remainder of the postmortem examination gave results within normal limits which were noncontributory.

Microscopic Study.—The right lung showed expansion of the alveoli, with pronounced thinning of the alveolar wall and many ruptured alveoli. Small, scattered areas of ruptured alveoli were interspersed with areas of atelectasis of unexpanded lung. The bronchi were clear and the mucosa intact. About the arteries, in their sheaths and in the lymph channels surrounding them, were dilated spaces containing air. Air spaces were also seen under the pleural surface.

The left lung showed evidence of expansion in small focal areas. The remainder of the lung was atelectatic and congested. The alveolar walls were relatively thick, and the epithelium lining the alveoli was of low cuboidal type. The sheaths about the vessels showed no air spaces.

The kidneys showed no abnormalities. An active nephrogenic zone with evidence of new tuft formation was present.

The liver showed excellent preservation of the lobule and the hepatic cells. There were many scattered areas of hematopoiesis about the periportal areas. The spleen also had active hematopoiesis in the sinusoids. The prostate showed squamous metaplasia of the ducts, with some keratinization of the utriculus prostaticus, a common observation in the newborn male as an effect of maternal estrogens on

the reactive tissue, the homologue of the vagina. The remainder of the tissues was essentially normal and noncontributory.

The final pathologic diagnosis was interstitial emphysema of right lung, posterior pneumomediastinum, emphysema of deep fascial layers of neck, right pneumothorax, pneumopericardium, pneumoperitoneum (from clinical history), tamponade of large veins, congenital atelectasis of the left lung, prematurity (thirty-six weeks) and azygos lobe of the right lung.

COMMENT

This case demonstrates the pathways air takes in the human fetus after excessive pressure of air introduced by an intratracheal catheter. It may be presumed that the catheter was introduced into the right main bronchus, as the left lung was atelectatic while the right lung was completely expanded. The concept of the mechanism for pneumothorax was developed and amplified by Macklin and Macklin.[2] Until C. C. Macklin performed the osmic acid fume fixation of the lung, it was thought that pneumothorax resulted from pleural rupture.

Tow [3] stated that "forced breathing causes rupture of the emphysematous bleb and if this is located at the periphery of the lung as it usually is, a pneumothorax follows." Silver in 1939 [4] defined spontaneous pneumothorax in the newborn as "emphysema which is followed by rupture of the lungs." The present case calls attention again to the fallacy that rupture of the pleura directly overlying an emphysematous bleb precedes pneumothorax in the newborn. It is also the first case reported in the literature which repeats in the human subject the same conditions which C. C. Macklin used in his experiments on overinflation of the lungs of the cat.[5]

Pathways of Air Dissection.—With increased intrapulmonary pressure there is overdistention of the alveoli with minute ruptures of the walls. The air enters the perivascular sheaths and the lymph channels about the vessels. Hot fluid gelatin containing carmine particles was shown to pass through the minute ruptures in the alveoli into the underlying vascular sheaths. The small particles of carmine remained piled up along the alveolar wall. When the ruptures were larger, the carmine appeared in streams of particles leading from the mass of gelatin in the perivascular sheaths.[6] The air travels in the same manner through the perivascular sheath toward the hilus. Here it takes the path of least resistance and passes into the mediastinum. The air not only travels along the vessels but dissects along the interlobular septums, through which it reaches the surface of the lung to form blebs under the visceral

2. Macklin, M. T., and Macklin, C. C.: Medicine **23**:281, 1944.

3. Tow, A.: Diseases of the Newborn, New York, Oxford University Press, 1937.

4. Silver, H. B.: Spontaneous Pneumothorax in the Newborn: Report of a Case in Which the Mechanism Was Demonstrated, Am. J. Dis. Child. **57**:907 (April) 1939.

5. Macklin, C. C.: Canad. M. A. J. **36**:414, 1937.

6. Macklin, C. C.: Canad. M. A. J. **38**:401, 1938.

pleura. Subpleural blebs may also result from rupture and coalescence of air in surface alveoli. The pleura, however, does not ordinarily rupture. The air travels along the vascular sheaths to the hilus of the lungs and thence to form pneumomediastinum.[8]

Subcutaneous emphysema is a result of direct extension of the air from the mediastinum through the fascial planes of the neck. With the realization that pneumomediastinum is the step following interstitial emphysema of lung and the one preceding pneumothorax, it need no longer be considered an unusual feature when subcutaneous emphysema is observed associated with spontaneous pneumothorax.

Pneumothorax develops with rupture of the mediastinal pleura. Thus, the air travels a circuitous route to the pleural cavity via the mediastinum. Although the pneumothorax is usually on the same side as the emphysematous lung, it need not necessarily be so. In the cat both mediastinal pleurae were shown to rupture simultaneously.[6] Furthermore, it was shown that with a change of position in newborn human cadavers the rupture site may seal off, and, with continued inflow of air, the mediastinal pleura of the opposite side can rupture to produce bilateral pneumothorax.[8]

Dissection of the air along the aorta through the hiatus of the diaphragm produces a pneumoretroperitoneum which can rupture through the peritoneum to produce a pneumoperitoneum. Thus, we can explain the distention of the abdomen without a ruptured abdominal viscus seen in the present case.

Pneumopericardium is a result of the air dissecting along the great vessels toward the heart. This has never before been reported as a complication of pneumothorax in the newborn. Perhaps the extremely high pressure used in this case explains the uncommon mode of air dissection.

The pressures required to produce pneumomediastinum and pneumothorax are far below that required to rupture a bleb on the surface of a lung. DeCosta [9] reported that intrapulmonary pressure of 18 to 20 mm. of mercury was sufficient to produce a bullous emphysema, while 100 mm. of mercury pressure would not rupture the pleural surface in the dog. In the human fetus it required 60 to 85 mm. of mercury to rupture the pleura, the tear invariably occurring at the hilus of the lung.[8] With insertion of a needle into the mediastinal space, pressure of only 40 mm. of mercury was required to rupture the mediastinal pleura to produce pneumothorax.[8] This rupture usually took place at the inferolateral margin of the thymus, and, once it had occurred, a much lower pressure was sufficient to continue the filling of the pleural cavity with air. Thus, the danger zone of intratracheal insufflation is 18 mm. for the production of pneumomediastinum and 40 mm. for the production of pneumothorax.

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7. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonic Blood Vessels from Alveoli to Mediastinum: Clinical Implications, Arch. Int. Med. **64**:913 (Nov.) 1939.

8. Goldberg, J. D.; Mitchell, N., and Angrist, A.: Am. J. Surg. **56**:448, 1942.

9. DeCosta, E. J.: Am. J. Obst. & Gynec. **39**:578, 1940.

The pockets of air along the perivascular sheath have an important effect other than the creation of a pathway for the air. With distention of the sheaths, as air pressure is increased or egress of air is impaired, the air compresses the pulmonary blood vessels and interferes with the flow of blood in the part, particularly the flow of venous blood. With extension of the air to the sheaths of larger vessels, there is general occlusion of the venous return and tamponade then becomes the important complication. Pulmonary interstitial emphysema with tamponade of the circulation was the cause of death in a 2½ year old child.[10] The child had aspirated peanuts, with occlusion of the right main stem bronchus. Compensatory emphysema of the left lung occurred with resultant mediastinal emphysema. Gumbiner and Cutler[11] described a case of mediastinal emphysema in a newborn infant demonstrated on lateral roentgenogram of the thorax. Aspiration of air from the anterior mediastinum gave complete relief of the circulatory disturbance. Aspiration in such circumstances is an emergency measure, and delay may result in death. These authors attempted to explain some of the supposed thymic deaths on the basis of mediastinal emphysema. In our case the distention of the azygos system of veins was postmortem evidence of venous occlusion.

The extension of air into the neck and the retroperitoneum provides the usual escape routes of the air. Should they fail, and pneumothorax fail to appear, the interference in the circulation arising from the air bubbles of varying size about the pulmonary arteries and veins, the great vessels of the mediastinum and the heart may be fatal. Strongin,[12] on aspiration of air from the mediastinum by this procedure, obtained immediate improvement of circulation in a newborn infant with tension pneumothorax. It is quite conceivable that other cases reported in the literature with fatality[5] might have resulted in recovery had the air pressure in the pneumomediastinum been relieved. Strong[13] made the point that a lateral roentgenogram should not be omitted in cases of dyspnea in the newborn. This point is well taken, as the lateral roentgenogram is the most satisfactory method of demonstrating mediastinal emphysema.

SUMMARY

A case is reported in which an excessively high pressure of more than 300 mm. of mercury was accidentally connected to an intratracheal catheter to resuscitate a newborn infant. The pathways for the air to produce emphysema, pneumomediastinum, pneumoperitoneum and pneumopericardium are demonstrated and discussed.

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10. Fisher, J. H., and Macklin, C. C.: Pulmonic Interstitial and Mediastinal Emphysema: Report of a Fatal Case in Which the Emphysema Occurred in a Child as a Result of the Aspiration of Peanut Fragments. Am. J. Dis. Child. **60**:102 (July) 1940.

11. Gumbiner, B., and Cutler, M. M.: Spontaneous Pneumomediastinum in the Newborn, J. A. M. A. **117**:2050 (Dec. 13) 1941.

12. Strongin, H.: Tension Pneumothorax in Newborn: Report of Case with Recovery, Am. J. Dis. Child. **56**:110 (July) 1938.

The pressures required to produce emphysema and pneumothorax via these pathways are 18 and 40 mm. of mercury. This is low compared to a minimum of 80 mm. of mercury pressure required to rupture a bleb on the surface of the lung. The maximum pressure safe for resuscitation of the newborn is slightly less than 18, or approximately 15, mm. of mercury. Tamponade of the circulatory system as a complication of mediastinal emphysema is also discussed, and the importance of mediastinal aspiration as an emergency and life-saving measure is stressed.

This case repeats in a human subject the same conditions which C. C. Macklin used in his experiments of overinflation of the lungs in the cat. The pathways of the air taken in the cat were observed to apply in the human being.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

A Diet of Carrot and Powdered Algarroba Bean in the Treatment of Diarrhea in Infants. P. Rohmer, R. Sacrez and J. A. Rohmer, Arch. franc. de pédiat. **38**:214, 1946.

The authors assert that the inclusion of algarroba bean powder in carrot soup, employed in the management of digestive disturbances of infants, constitutes a genuine contribution to the therapy of that period. Fruit and vegetable products have been used in the treatment of diarrhea since 1903; their value has been attributed to the pectin and cellulose content. Algarroba adds another element, known as lignin. Results of using algarroba bean in carrot soup for patients with simple and grave dyspepsias, as well as for those with enteritis, have been very satisfactory.

Amesse, Denver.

Peculiarities in Pathogenesis and Treatment of Anemia in Children with Alimentary Dystrophy. E. I. Fridman, Pediatria **52**:23 (April) 1944.

During the siege of Leningrad in 1942 and 1943 nutritional anemia secondary to alimentary dystrophy and avitaminoses became a major pediatric problem. It is of interest that only 7 or 8 cases of frank pellagra were observed by the author in a series of 600 children with scurvy and in an equal number of children with rickets. The author points out that the usual methods of treatment of nutritional anemias are frequently ineffective in the presence of alimentary dystrophy and vitamin deficiency diseases. However, improvement of the diet and administration of multivitamin preparations, in addition to specific measures to combat the anemia, yielded good results in most cases observed by the author.

There were, however, a number of patients in the author's series, especially those presenting the symptom complex of Jaksch-Hayem anemia, who failed to respond even to this combined form of therapy. In these patients recovery was achieved by the administration of a purified solution of liver known as "campolon." Five case reports, illustrating the effect of "campolon," are presented in detail. The author's conclusions are as follows: 1. "Campolon" is a valuable aid in the treatment of severe nutritional anemia, as well as alimentary dystrophy, especially when associated with the predominant symptoms of vitamin B deficiency. 2. The antianemic effect of "campolon" is most noticeable in hyperchromic anemia, with a relatively high color index. 3. "Campolon" stimulates the production of platelets as effectively as do blood transfusions. 4. A deficiency of Castle's intrinsic factor (a component of the vitamin B complex) in the food is important in the pathogenesis of hyperchromic anemia of alimentary origin. "Campolon" appears to be rich not only in Castle's intrinsic factor but also in other components of the vitamin B complex. 5. In the treatment of hypochromic anemia associated with alimentary dystrophy, "campolon" therapy must be supplemented with other measures which will bring about a rise in hemoglobin, such as administration of iron and ascorbic acid and blood transfusions.

Boder, Los Angeles.

ASSOCIATION OF VITAMINS AND MINERAL SALTS IN TREATMENT OF CHILDREN WITH DISTURBANCES OF NUTRITION. ANGELO GALEONE, Pediatria **54**:555, 1946.

On the basis of already known data regarding the importance of certain vitamins and mineral salts for the development of men and animals, and the biologic synergy of the two groups of substances, the author studied the effects of vitamins A and D and of the most biologically important mineral salts in a group of children who were undernourished and underdeveloped in consequence of insufficient food. There was improvement in the general condition, development, weight and blood crasis, and in any case the results were much more encouraging than those obtained in another group of undernourished and underdeveloped children in poor general condition who were treated with common cod liver oil.

FROM THE AUTHOR'S SUMMARY.

CHLORIDE CONTENT OF BLOOD OF NORMAL AND PREMATURE INFANTS. D. VITTORIA BORI and MARY CRISALLI, Riv. di clin. pediat. **40**:627 (Oct.) 1942.

Analyses were made of the chloride levels and total chlorine content of the capillary blood of 12 normal and 22 premature infants. Both chloride and total chlorine were lower in the jaundiced infant and higher in the scleremic infant than in the normal infant. Less constancy in the results was shown with the young premature infant than with the infant as he grew older or with the full term infant.

HIGGINS, Boston.

Hygiene; Growth and Nutrition; Public Health

A DEVELOPMENTAL GRAPH FOR THE FIRST YEAR OF LIFE. C. A. ALDRICH and M. A. NORVAL, J. Pediat. **29**:304 (Sept.) 1946.

The average neuromuscular achievement of 215 unselected infants during the first year is graphically represented. Observations from similar studies performed by other workers are briefly discussed and compared.

GRULEE JR., Minneapolis.

MEDICAL PROGRESS: NORMAL GROWTH AND DEVELOPMENT DURING ADOLESCENCE (CONCLUDED). HAROLD C. STUART, New England J. Med. **234**:732 (May 30) 1946.

The author discusses adolescent changes in physiologic functions, such as basal metabolism prepubescent and postpubescent, caloric intake, muscular growth and cytologic changes in the blood. Also he considers the influence of the endocrine glands, thyroid, pituitary, adrenals, ovaries and testes, together with the results of studies in calcium and nitrogen retention.

The author points out the advantages and helpfulness of medical supervision of infants, children and adolescents, as contributing much toward better health and toward a higher standard of physical fitness at maturity.

GENGENBACH, Denver.

Newborn

RH FACTOR AND ERYTHROBLASTOSIS FETALIS. CARL L. LANGFORD, New Orleans M. & S. J. **99**:169 (Oct.) 1946.

A case of erythroblastosis fetalis successfully treated with several transfusions of ORh-negative blood is reported. The first transfusion of 15 cc. was given into the cord at the time of delivery. Subsequently, 12 cc. was given intravenously,

followed by 30 cc. intraperitoneally daily for four days. Although treatment was successful, the author, in retrospect, expressed the belief that larger transfusions at the beginning, possibly of 60 to 75 or 100 cc. given daily for the first three days, would have prevented the severe anemia. With such large transfusions, care should be exercised to prevent embarrassment of the circulation.

When a pregnant mother is Rh negative, the father and the other children should be checked. If the father is Rh negative, the mother's blood should be frequently checked. If titer is increasing and the child is viable, it should be delivered early by section.

BERKLEY, Beverly Hills, Calif.

DISCUSSION ON NEONATAL INFECTIONS. BERYL CORNER, Proc. Roy. Soc. Med. **39**:383 (May) 1946.

With few exceptions pediatricians have largely devoted themselves to the problems of infancy that occur after the first two or three weeks of life. It has become increasingly clear that since the foundations of infant health are laid in the first few weeks of life the study of the neonatal period is of great importance. One of the first problems that confronts the pediatrician is that of neonatal infection. Gastroenteritis and the infections of the respiratory tract of the neonatal period are the most important conditions, while pathogenic staphylococci are responsible for many of the lesions.

The author in her paper discusses fully the incidence and prevention of infections and special technics used in their treatment.

The ophthalmic aspect of neonatal infections is discussed by Dr. Arnold Sorsby.

WILLIAMSON, New Orleans.

INFANT MORTALITY AS SHOWN AT AUTOPSY. (ABORTIONS AND NEONATAL MORTALITY.) GIUSEPPE ZANGRI, Pediatria **54**:580, 1946.

From the data obtained from the Institute of Pathologic Anatomy of Catania University on postmortem examinations of 3,187 subjects of various ages during the years 1923 to 1942, the author noted that the abortive products, the stillborn and the newborn children, who died during the first four weeks of life constituted nearly one fifth of the autopsy material. In this statistical study he examines the various causes and frequency of abortion and stillbirth.

Having summarized the most interesting cases, he concludes that more efficacious prenatal care and more correct assistance during the delivery could reduce particularly the high mortality due to trauma and asphyxia.

FROM THE AUTHOR'S SUMMARY.

APPLICATION OF PICKWORTH'S METHOD TO THE STUDY OF INTRACRANIAL HEMORRHAGE IN ASPHYXIATED PREMATURE INFANTS. MARGHERITA BERTOLLI, Riv. di clin. pediat. **41**:219 (April) 1943.

Pickworth's method makes use of benzidine in the histologic examination for hemorrhage in nerve tissue. Bertolli applied this method in a study of the tissue of the brains of 7 infants who died of neonatal asphyxia.

HIGGINS, Boston.

THE ANTITRYPTIC PROPERTY OF BLOOD SERUM OF FULL TERM AND PREMATURE INFANTS. D. VITTORIA BORI and M. MORETTA, Riv. di clin. pediat. **41**:430 (Aug.) 1943.

Observations on the blood of 12 premature and 12 normal infants revealed that the antitryptic potency was greater in the blood of the premature infants. The suggestion is offered that this increase is an expression of the increased cellular metabolism in the premature infant.

HIGGINS, Boston.

OBSERVATIONS ON 51 CASES OF SEPTICEMIA. PEDRO ARAYA CHIAPPA, Arch. argent. de pediat. **25**:219 (April) 1946.

Fifty-one cases of septicemia (26 of boys, 25 of girls) among newborn infants up to 3 months of age, who were observed in the pediatric clinic from 1940 to June 1945, are analyzed. The rise in the frequency of sepsis in the past two and a half years is apparent rather than real. It is due to increased interest and better understanding of the clinical picture. Forty-one (85.4 per cent) of the 48 cases in which the clinical signs were apparent in the first three months of life occurred during the first month; in 32 of these, signs of infection were seen before the tenth day of life.

Among the symptomatic forms of the infection the authors recognized pseudoparalysis, pseudotetanus, erysipelas, adiponecrosis, signs of encephalosis, mumps, involvement of the preauricular ganglion and, especially, the lesions of bone, osteochondritis, osteomyelitis and periostitis identical with those caused by the spirochete of syphilis, although the serologic reactions of the parents and babies were negative.

Choroiditis, as a sign of congenital syphilis, was shown to be of little value in the ophthalmologic examination. Attention is called to the rare occurrence of peritonitis. The most frequent portal of infection was the umbilical cord; then, in order, the bucconasal, the pharyngeal and the intestinal mucosa were affected. Of the cases of sepsis, 59.4 per cent occurred among infants born in maternity hospitals.

In 42 cases (8.3 per cent of the total 51) the causative agent was sought in the pus or blood; 31 (73.8 per cent) yielded pathogens; 12 showed beta hemolytic streptococci; 9 Staphylococcus (7 citreus, 2 aureus); 3 Salmonella schottmülleri (paratyphoid B); 3 Escherichia coli; 1 (each) of Salmonella enteritidis, Pneumococcus, Gonococcus and Proteus mirabilis.

Blood cultures were made in 28 cases; 12 were positive for pathogenic organisms, 14 were negative and 2 contaminated. Attention is called to delay on the part of the mothers in seeking medical care in these 51 cases; only 17 mothers consulted a physician before the fifth day of illness. The other 34 (66.7 per cent) sought medical aid between the fifth and the fortieth day.

The fatality rate was 49 per cent. The death rate by years and months was highly variable.

Sulfonamide therapy was used, always accompanied with transfusion of fresh blood in accord with standard dosage. In August 1944, penicillin, in doses of 7,500 Oxford units per kilogram of body weight, was added to this treatment.

ROJAS, Boston.

VITAMIN K SENSITIVITY TEST IN NEONATAL JAUNDICE. K. BIERING-SÖRENSEN and H. DYGGVE, Nord. med. (Hospitalstid.) **26**:929 (May 4) 1945.

The rise of the prothrombin level in the blood of 42 icteric newborn infants after injection of vitamin K was the same as that in 8 nonicteric infants after the identical treatment. The authors conclude that this test does not suggest any insufficiency of the liver in infants with icterus neonatorum.

WALLGREN, Stockholm, Sweden.

AVITAMINOSIS K AND RETINAL HEMORRHAGE IN THE NEWBORN. HERLUF WILLE, Nord. med. (Hospitalstid.) **26**:1188 (June 8) 1945.

Retinal hemorrhages occurred in 42.4 per cent of the group of 594 newborn infants examined. In no child were any ophthalmoscopic changes observed after the resorption of the hemorrhages. Of 316 newborn infants whose mothers had

received vitamin K before delivery, only 31 per cent displayed retinal hemorrhages. The author concludes that avitaminosis K probably is of etiologic importance in the development of these hemorrhages.

WALLGREN, Stockholm, Sweden.

Acute Contagious Diseases

THE MENINGOCOCCAL-ADRENAL SYNDROME. J. MACDONALD HOLMES and J. MACFARLANE COWAN, Lancet **1**:13 (Jan. 6) 1945.

The meningococcic-adrenal syndrome may occur with or without meningeal involvement. It is important to watch carefully all cases of severe meningococcic meningitis for the development of this picture. Rapid fall in blood pressure is the most reliable symptom, other symptoms being collapse and the rapidly developing purpuric lesions.

The authors report on 5 children. Three of these children (aged 4, 8 and 15 years, respectively) came from one family of 6 children and were admitted to the hospital within seventy-two hours. Three of the 5 had meningeal involvement. Four of the 5 died shortly after onset. One girl, aged 21 years, recovered. She did not have hemorrhagic cutaneous lesions but the presence of this syndrome was suspected because of fall in blood pressure and low blood sugar. She was treated with sulfapyradine intravenously, sulfathiazole orally and desoxycorticosterone acetate intramuscularly.

The authors are of the opinion that the basis of the syndrome is acute circulatory collapse and that the most important phase of treatment lies in combating this circulatory failure.

HODGES, Cleveland.

WATERHOUSE-FRIDERICHSEN SYNDROME IN MENINGOCOCCIC SEPSIS. RAFFAELE STIGLIANI, Riv. di clin. pediat. **44**:385 (July) 1946.

Four cases of generalized purpura, with small hemorrhages of the adrenal glands (which were macroscopically visible), and 1 case of generalized purpura, with destructive bilateral hematoma of the adrenal glands and clinical symptoms of grave septicemia, are described.

FROM THE AUTHOR'S SUMMARY.

ISOLATION AND CULTIVATION OF THE AGENT OF INFECTIOUS MEGALERYTHEMA. LELIO NASSI, Riv. di clin. pediat. **44**:449 (Aug.) 1946.

The author describes his efforts to isolate and cultivate the etiologic agent of the fifth exanthematous disease, infectious megalerythema. He used intracorneal inoculation in the rabbit and intra-allantoic insemination of developing chick embryo with plasma and mucous filtrate from the pharynx of patients. No lesions were observed in the cornea, while the allantois of the chick embryo showed characteristic macroscopic and microscopic alterations which could be reproduced in successive cultures. The neutralization test with serum from a convalescent patient showed a positive reaction. The author is of the opinion that a specific filtrable virus is the agent of the disease. Comments are made on the epidemic observed in Florence in 1945.

FROM THE AUTHORS' SUMMARY.

INFECTIOUS MEGALERYTHEMA. ANGELO INGIULLA and ROBERTO DECIO, Riv. di clin. pediat **44**:544 (Sept.) 1946.

During an epidemic of infectious megalerythema in the city of Florence, Italy, the authors carefully studied 50 patients from a clinical point of view with labora-

tory tests and pathologic examinations. Their observations are reported, together with a complete review of all the most important facts known and written about this disease.

The personal ideas of the authors on some still obscure points are described in a final synthesis, with a discussion on the real character of this uncommon exanthematous syndrome.

FROM THE AUTHORS' SUMMARY.

THE EPIDEMIC OF DYSENTERY IN 1945 IN BUDAPEST. J. CSAPÓ, Orvosok lapja **2**:241 (Feb.) 1946.

Dysentery was seen earlier this year than in previous years. Patients with dysentery were brought into the St. Ladislas epidemic hospital in Budapest, Hungary, in previous years mostly during the months of July and August. In 1945, however, the epidemic broke out in May and terminated suddenly at the end of July. From March 1 to September 1 the mortality rate among 443 infants and children who were treated in the hospital was 50 per cent. In this year the remarkable fact was that not only infants but even older children showed a higher mortality rate and their illness was of a severer nature. Some of the infants died from severe acute symptoms caused partly by starvation, for their food was nothing but mixtures of carbohydrates and potatoes. The hospital had no means of feeding even its convalescent patients. In Hungary dysenteric infections are caused mostly by the Flexner bacillus (Shigella paradysenteriae), but in this year infection with Shiga-Kruse bacillus (Shigella dysenteriae) prevailed.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

THE VIRUS OF CHICKENPOX. P. FERENCZ, Orvosok lapja **2**:497 (April) 1946.

Immunization against chickenpox is possible. The water-clear vesicular fluid should be aspirated and diluted with isotonic solution of sodium chloride in a dilution of 1 : 20. It should be given intracutaneously in a quantity of 0.05 cc. to the infected child. Protection can be obtained only when the injection is given within two days after exposure. From seven to twelve days after the injection a small vesicle or a slight infiltration develops, showing that the child has become immune to chickenpox. Examinations were made on 400 children, and Ferencz is well satisfied with the results. The virus of chickenpox is more resistant than the virus of poliomyelitis but less resistant than the virus of vaccination. The vesicular fluid in chickenpox can be used as the antigen in the complement fixation test for its specific reaction. Ferencz expresses the belief that the virus of chickenpox in the beginning causes a cutaneous eruption and later mixed symptoms on the skin and in the nervous system (herpes zoster), with finally only nervous manifestations. Of 18 cases of ischiatic neuritis the reaction to the complement fixation test with chickenpox antigen was positive in 4.

GÖRGÉNYI-GÖTTCHE, Budapest, Hungary.

SPOTTED FEVER (EPIDEMIC CEREBROSPINAL MENINGITIS). HOLGER E. NIELSEN and GREGERS NÖRBY, Ugesk. f. læger **107**:503 (June 28) 1945.

Eighteen cases of meningococcic septicemia in children, aged 6 months to 10 years, are reported. The children were ill with fever and purpuric spots in the skin. Then signs and symptoms of meningitis developed, with meningococci demonstrable in the pleocytotic liquor. Treatment consisted of sulfonamide compounds in large doses. Five of the children died.

WALLGREN, Stockholm, Sweden.

Chronic Infectious Diseases

CONGENITAL TUBERCULOSIS. ERNEST LOEWENSTEIN, Am. Rev. Tuberc. **51**:225 (March) 1945.

Congenital infection with tuberculosis takes place through the placenta and occurs, therefore, not earlier than the fourth month of pregnancy. Germinal infection plays no role. Placental infection is far more frequent than is generally realized, occurring even in mothers with small lesions in the lungs. It has been found in as high as 25 to 43 per cent of tuberculous mothers. Infection of the infant occurs only by the hematogenous route, which may be by way of the porta hepatis to the liver, where the bacilli may be filtered out, or by way of the ductus venosus, vena cava, right auricle and pulmonary arteries, and perhaps by the ductus arteriosus into the general circulation. Great variation exists in the amount of infectious material which reaches the infant. In case of a single invasion during labor, owing to expression of the placenta by uterine contractions, only a minimum number of bacilli may reach the infant, and may be effectively arrested in the liver. When the influx of bacilli extends over a longer period, all barriers in the infant may fail, and the infant is born dead or dies of miliary tuberculosis a short time after delivery. Loewenstein demonstrated tubercle bacilli in the blood of 3 infants who remained well. Bacilli were seen in the blood from the umbilical cord of 9 infants of 59 tuberculous mothers; 1 baby died of tuberculosis. Cord blood containing tubercle bacilli was obtained in 2 of 201 apparently healthy mothers; the 2 babies remained well. Autopsy of congenitally infected babies may show no gross lesion, but sections, and especially cultures of the heart blood, may reveal the presence of bacilli. The reaction of such babies to tuberculin may remain negative for a long time, even for those proved to be tuberculous at autopsy.

SMITH, Ogden, Utah.

TUBERCULOSIS IN CHILDREN. J. SCHWARZ, Am. Rev. Tuberc. **52**:392 (Nov.) 1945.

This paper records an extensive study of postmortem material from hospitals in Santiago, Chile. The prevalence of tuberculosis in that country is evidenced by the mortality rate of 241 per hundred thousand population (mortality in the United States 53.6 per hundred thousand population). This rate is accounted for principally by the prevalence of poverty, the low standards of living, the lack of hygiene and the defects in sanitary legislation. The extent of the disease is reflected in the high percentage of infected children and the high death rate from tuberculosis in this age group.

Comparing his postmortem observations with those of other investigators (especially Terplan, in Buffalo, N. Y.), Schwarz noted significant variations. In Buffalo most children who died of tuberculosis had only hematogenous generalization; in his material bronchial spread combined with hematogenous dissemination was frequently encountered. Especially in this group, he saw numerous Ghon foci, with cavitation and extensive involvement of the bronchial mucosa. It is chiefly the size of the primary focus and the age of the child which determine central liquefaction and the formation of a cavity. Size alone, however, without liquefaction is of no prognostic significance. Only the formation of a primary cavity indicates a poor prognosis. The number of children with primary cavities decreases rapidly after 2 years of age.

Only 2 cases of atelectasis (epituberculosis) were seen. This condition, in his opinion, is always accompanied with tuberculous infection of the affected lobe, and the prognosis will depend on the general evolution of the tuberculous process.

Bronchogenic dissemination in his material was shown to have been of four types: perforation of the bronchial wall by caseated lymph nodes; bronchial perforation related to pulmonary cavities; ulceration of bronchial mucosa, with or without perforation, and bronchogenic dissemination without macroscopic involvement of bronchial mucosa.

Tuberculous meningitis is generally observed in cases of early hematogenous generalization. Its frequency diminishes after the third year of life. Schwarz considers the presence of tuberculomas in the brain of great importance for the formal pathogenesis of tuberculous meningitis, because of the frequency of tuberculoma, the presence of tuberculoma without meningitis, the difference in the ages of the nodules of meningitis nodules and those in other organs and the absence (almost without exception) of miliary tubercles in the substance of the brain.

SMITH, Ogden, Utah.

PLASMA α-AMINO ACID NITROGEN AND SERUM LIPIDS OF SURGICAL PATIENTS. EVELYN B. MAN, PATRICIA G. BETTCHER, CLAIRE M. CAMERON AND JOHN P. PETERS, J. Clin. Investigation **25**:701 (Sept.) 1946.

Data were collected on 40 patients during preoperative and postoperative states, in an attempt to correlate reduction in plasma amino acids and nitrogen losses usually seen in disease and after trauma.

The plasma α-amino-acid nitrogen fell sharply after operation and remained low until recovery was well advanced. Even with greatly increased nitrogen catabolism obtained with high protein feedings, and in the face of increased negative nitrogen balances, the plasma α-amino-acid nitrogen values remained low. In patients with initial plasma α-amino-acid nitrogen levels of 4.0 mg. per hundred cubic centimeters or over (normal values), the postoperative fall was directly proportional to the severity of operation. In already chronically ill or debilitated patients whose initial α-amino-acid nitrogen levels were below 4.0 mg. per hundred cubic centimeters, there may be little, or no, fall in amino acid nitrogen after operation.

Serum lipid fractions, total and free cholesterol, lipid phosphorus and fatty acids decreased proportionally by small, but significant, amounts after injury. The authors point out that the same type of change in lipid components occurs in association with hepatic disease.

WILLIAM A. BRODSKY, Cincinnati.

SUPPURATIVE ADENITIS AFTER VACCINATION WITH BCG. GERMAIN BLECHMANN AND JACQUES PERRET, Arch. franç. de pédiat. **3**:164, 1946.

This report was presented at a session of the Paris Pediatric Society. It concerned a female infant 10 months of age whose father had active tuberculosis and whose paternal grandmother died of the disease. The baby was consequently vaccinated with BCG by scarification. The patient was breast fed and thrived up to the age of 2½ months. At that time slight swelling was noted in the right groin; simple adenitis was considered, but for two weeks after this sign appeared there was no change. The tumefaction was about the size of a cherry, round, elastic, movable and irreducible. It resembled a cyst in the vestigial canal of Nück. The cutaneous reaction to the tuberculin test at this time was 1 plus. This condition persisted for the next six months, when suddenly the swelling increased; there was fluctuation, and the mass became adherent to the surrounding tissues. A small gland was felt beneath. The infant was then referred to the service of Dr. Bretey, at the Pasteur Institute, who made the following report: "On puncture I obtained 3 cc. of thick pus, which was immediately examined

and found sterile. Inoculation of a guinea pig and growth on suitable cultures were instituted. It was concluded that the condition was a reaction from BCG scarification, although I have seen only 50 cases of such response in more than 50,000 scarifications."

The abscess finally discharged spontaneously. Recovery was complete, as shown by the normal gain in weight and the appearance of nothing abnormal on roentgenograms.

AMESSE, Denver.

Diseases of Blood, Heart and Blood Vessels and Spleen

CRITERIA OF EOSINOPHILIA. GEORGE DISCOMBE, Lancet **1**:195 (Feb. 9) 1946.

The author describes a method by which the eosinophils can be stained by eosin Y and easily differentiated from leukocytes in a hemacytometer chamber by the use of strong light. The author gives statistical reasons for the increased accuracy of this method over the count made from stained smears. The normal range of eosinophils is 0 to 280 per cubic millimeter. Not more than 1 per cent of normal subjects should have counts above this value.

HODGES, Cleveland.

PENICILLIN IN SUBACUTE BACTERIAL ENDOCARDITIS. RONALD V. CHRISTIE, Lancet **1**:369 (March 16) 1946.

The data are based on 147 patients treated in 14 centers in the United Kingdom. The author concludes that the duration of treatment is just as important as the daily dose and recommends that 500,000 units a day be given for twenty-eight days to previously untreated patients. Relapses after long courses of treatment are rare within fifty days from cessation of treatment; they are frequent when the duration of treatment has been less than ten days. Once relapse occurs, treatment is more difficult. The recommended dose is 500,000 units for forty-two to fifty-six days. The resistance of the infective organism appeared to play only a small part in the difficulty of treating patients who had relapses. The author states that only those organisms with resistance to penicillin ten times that of standard staphylococcus (Oxford) are of clinical importance. The figures on which this statement are based are few. Even with optimal treatment there will still be a definite mortality due to heart failure, uremia and major emboli.

HODGES, Cleveland.

LEUKEMIA TREATED WITH URETHANE. E. PATERSON, A. HADDOW, I. A. THOMAS, and J. M. WATKINSON, Lancet **1**:677 (May 11) 1946.

Urethane was shown to have a growth-inhibiting effect on animal tumors. A trial was made in persons with leukemia. Doses comparable to those used in animals could not be given because of toxic symptoms (nausea and vomiting). For the 4 children studied the dose was 1 to 3 Gm. per day for eight to fifty-six days. Although several adults showed a fall in white blood cell count and shrinkage of spleen and lymph nodes, only 1 child, a boy of 11 years with myeloid leukemia, appeared to benefit. Three children with lymphatic leukemia, aged 3, 6 and 8 years respectively, showed little improvement. The results were compared with those from deep roentgen ray treatment, and in the opinion of the authors the two methods were about equally effective.

HODGES, Cleveland.

HEMOLYTIC ICTERUS (ACHOLURIC JAUNDICE), CONGENITAL AND ACQUIRED. K. E. BOORMAN and B. E. DODD, Lancet **1**:812 (June 1) 1946.

The authors discuss the difficulty of distinguishing between the congenital and the acquired forms of acholuric jaundice either by family history or by tests for autohemolysins. Both states are characterized by hemolytic anemia, jaundice without bilirubin in the urine, anemia, splenomegaly, reticulocytosis, spherocytosis and increased fragility of the erythrocytes to hypotonic saline solution. Splenectomy is less effective in the acquired form.

The authors state that they distinguish the congenital from the acquired types by testing the washed red blood cells of the patient against antihuman rabbit serum. A 2 per cent suspension of washed erythrocytes was mixed with an equal volume of "suitably diluted" rabbit serum and allowed to stand at room temperature for "one hour or longer."

The cells of 17 patients with the congenital type were not agglutinated. The cells of 5 subjects with the acquired type were agglutinated. The cells of 5 patients with acquired hemolytic anemia, which did not meet the aforementioned criteria for "acholuric jaundice," were not agglutinated.

The authors state that sensitizing antibodies are present in the serum of patients with acquired acholuric jaundice but absent from the serum of patients with the congenital type.

HODGES, Cleveland.

CAPILLARY RESISTANCE IN NORMAL INFANTS. G. STEGAGNO, Arch. ital. di pediat. e puericult. **11**:187, 1946.

The author studied capillary resistance in 50 healthy, well developed children, 24 days to 12 years of age, with gradual decompression (Hecht's test). He showed that the capillary resistance is independent of sex and is liable to variations due to age and zone of the skin tested.

Moreover, in the same zone capillary resistance presents, within limits, a variety of individual results. These individual variations, which are considerable in some zones, are kept in relatively narrow bounds in the area at the bend of the elbow, which is therefore considered the most suitable cutaneous zone for testing capillary resistance. Normal results for this region are: for the first three months of life, from —250 to —300 mm. of mercury; for the first two years of life, from —200 to —250 mm. of mercury, and after 2 years of age, from —200 to —150 mm. of mercury.

FROM THE AUTHOR'S SUMMARY.

Diseases of Nose, Throat and Ear

METROPOLITAN SPEECH CORRECTION. BERNEICE RUTHERFORD, LILLIAN READ and MYFANWY CHAPMAN, J. Speech Disorders **11**:131, 1946.

On a questionnaire 43 metropolitan school systems of over 100,000 population indicated that the lower the ratio of the school population to the number of speech clinicians the more adequate the speech correction service. The itinerant teacher plan and semiweekly service in elementary schools were typical and did not seem related to adequacy of service. Generally, there was inadequacy of service. A combination of clinical survey and referral from the classroom teacher, or a combination of referrals from many sources, were typical patterns. Speech correction service was given to almost 2 per cent of the elementary school population. Speech clinicians in most cities were required to have either specialized training or a degree in speech pathology. The questionnaire method of study allows for variation in interpretation.

PALMER, Wichita, Kan.

INDICES OF ACHIEVEMENT IN VOICE INSTRUCTION. FRANKLIN H. KNOWER and MARJORIE EMERSON, J. Speech Disorders **11**:159, 1946.

Four groups of students were studied: group 1 contained 17 students and group III 15 students; the controls were the 11 students of group II and the 13 students of group IV. All subjects were students of McKinley High School, Cedar Rapids, Iowa. Groups I and II were given a test of ability to use tonal symbols communicating emotion, moods and meanings, and each child read aloud a short passage one and a half to two minutes in length from Mark Twain's "The Oldest Inhabitant." Skilled college speakers received scores of 80 to 95 per cent intelligibility on these tests. Groups III and IV were tested completely by recording of material.

The authors concluded that the intelligibility test of tonal symbolism provides a practical test of achievement in the use of voice in speech instruction. Recordings of a short sample of oral reading are useful in providing an index of achievement in voice usage. Ratings of single trained but independent judges, although highly variable, are on the average higher than ratings of more generalized achievement in speech. The rating-rerating reliability of single judges was about the same as interrater reliability. The use of paired comparisons will reveal improvement not recognized when a single standard of judging records of achievement is employed. Voice improvement of far greater significance may be expected from a unit of concentrated instruction than can be expected from incidental voice instruction in a general speech unit. The students were not told that they were to be retested. Group I received instruction in motional meanings and special individual instruction in the whole material. Group II, a control group, was given simple work in informal speech activities. All the children in the four groups were retested six weeks later.

PALMER, Wichita, Kan.

EAR PIT (CONGENITAL AURAL AND PRE-AURICULAR FISTULA). IAN AIRD, Edinburgh M. J. **53**:498 (Sept.) 1946.

The author states that this malformation is inherited as an incomplete dominant, which shows a variable tendency, having no sex difference. He cites the observations of others that a curious feature of inheritance in a given family is the unilateral occurrence of the defect, one side being more often involved.

Of no great interest as a pathologic or surgical anomaly, such a malformation does illustrate certain principles in genesis, especially the development of the pinna, and is a contribution to the knowledge of occasional important chronic inflammations of the face. Not every pit or fossa in the pinna is congenital.

In uncomplicated cases the defect does not require treatment.

NEFF, Kansas City, Mo.

ARE SULFONAMIDE DRUGS APPROPRIATE IN ACUTE INFECTIONS OF THE UPPER RESPIRATORY TRACT? KAJ LARSEN, Ugesk. f. læger **107**:179 (March 1) 1945.

The author treated 170 patients with acute tonsillitis, 50 with peritonsillar abscess, 21 with ulcerative tonsillitis and 24 with infectious mononucleosis with sulfathiazole; an equal number was given sulfanilamide, and an equal number was given no sulfonamide compound at all. In no instance could the author get support for the assumption that the sulfonamide compounds had therapeutic effect. Untoward effects of the chemotherapeutic substances employed were observed in one fourth of the patients. He maintains that it is not appropriate to use sulfonamide therapy in diseases in which it is established that such treatment is ineffective.

WALLGREN, Stockholm, Sweden.

Nervous Diseases

COLLAPSED INTERVERTEBRAL DISCS FOLLOWING LUMBAR PUNCTURE. URSULA JAMES, Proc. Roy. Soc. Med. **39**:134 (Jan.) 1946.

A boy 4½ years of age underwent lumbar puncture in January 1945 during an investigation of fits. The fluid, which was withdrawn only after several attempts, was normal. One week later he was admitted to the hospital with a temperature of 104 F. He had been walking cautiously, with the hips flexed, and supported himself with his hands resting above the knees. He had been screaming at night. He sat up with difficulty. The lumbar portion of the spine was held rigid; loss of lordosis was noticeable. Roentgenogram showed the spine to be normal. Nine days later another roentgenogram of the spine showed narrowing of the space between the third and fourth lumbar vertebrae. Narrowing increased and the space between the fourth and fifth lumbar vertebrae was affected. Four weeks later there was erosion of the upper surface of the fourth lumbar vertebra and sclerosis surrounded it. The child was placed in a plaster bed in extension. Penicillin was given for six days because it was thought that the lesion might be low grade osteomyelitis. His temperature fell, and the general condition improved slowly. He was kept in the plaster bed for four months and walked about in a plaster jacket for two months. He was then and is still free from symptoms.

WILLIAMSON, New Orleans.

CHOREA: CLINICOPATHOLOGIC STUDIES IN A CASE. ANDRÉ-THOMAS and DE AJURIAGUERRA, Presse méd. **53**:575 (Oct. 27) 1945.

A boy aged 5½ years had severe chorea, with pronounced hypotonia and weakness of the left arm and leg; choreic movements were predominant on the left side. The chorea disappeared but cardiac failure developed, and the child died a year later. Autopsy showed extensive changes diffusely distributed throughout the cortical and subcortical centers, the hypothalamic region and the cerebellum. The authors find it difficult to reconcile the extreme chromatolysis that was present with the apparent functional recuperation which had occurred. Had death intervened at the height of the chorea, the anatomic changes would have been described as typical of the lesions producing the physical signs.

DAFFINEE, Melrose, Mass.

DIFFERENTIAL DIAGNOSIS OF MENINGORADICULITIS. EUGENIO SCHWARZ TIENE, Pediatria **54**:360, 1946.

The author reports several cases of meningoradiculitis with symptoms of extraordinary irritability. He takes into consideration the clinical picture of the disease and the differential diagnosis between it and acute anterior poliomyelitis (Heine-Medin disease).

This differential diagnosis becomes especially difficult in the presence of acute anterior poliomyelitis with meningeal or meningoradicular localization.

FROM THE AUTHOR'S SUMMARY.

TREATMENT OF CHOREA WITH DIPHENYLHYDANTOIN SODIUM ("DILANTIN"). J. M. SALA GINABREDA, A. MIMO GALINDO and J. L. VALENTI AGUILO, Acta pediat. españ. **42**:787 (June) 1946.

Treatment of 4 cases of chorea with diphenylhydantoin sodium is reported. Six cases previously had been reported (Sala Ginabreda). During the first week

of treatment 0.2 to 0.3 Gm. of the drug was given daily. This dose was increased to 0.5 or 0.6 Gm. During the second week with a maximum dose of the drug, evidences of toxicity appeared. The choreiform movements increased; the face was flushed, and there was general depression, vomiting and a morbilliform rash. All forms of medication were discontinued, and during the third week the choreiform movements diminished considerably. The picture was similar to that seen in treatment with phenyl-ethyl-hydantoin ("nirvanol"). In the authors' opinion cure was obtained more rapidly with diphenylhydantoin sodium than with any other form of medication (favorable effects were seen in fifteen to twenty days).

KEITH, Rochester, Minn.

Psychology and Psychiatry

THE CHILD IN SCHOOL. NAT P. BROOKS, Arch. Pediat. **63**:320 (July) 1946.

It is the author's opinion that too much time is spent "cramming" education into young children, with the result that nervous instability among young adults is on the increase. He points out that a child of 6 years in the first grade spends twenty-five hours a week in school and that by the time he reaches 12 years he spends thirty hours a week. He figures this to be, according to Young's table, "75 per cent over the safe, average hour allotment for the age of the pupil." If the children must stay in school that long, less time should be spent on actual educational work and more on social activity.

DAVIS, Denver.

THERAPEUTIC TECHNIQUES USED WITH A SPECIAL GROUP OF DISTURBED CHILDREN. ERWIN ANGRES, Illinois M. J. **89**:133 (March) 1946.

All kinds of psychiatric disturbances, ranging from rather mild behavior difficulties to persistent, violent and destructive behavior, are represented in a small group of 10 to 14 children at the Illinois Neuropsychiatric Institute.

A variety of psychiatric technics, coordinated into a total program, have been employed. These technics are used singly or combined, as need indicates. Different problems are presented to the therapeutists when children are hospitalized and under continuous care.

The emotional difficulties of these children have been so intense as to resist any kind of outpatient management. The first problem is to provide an environment which approximates as closely as possible that of a family, and a healthy atmosphere in which the child can grow. Any institutional placement has inherent disadvantages. In the program as set up, only the psychiatrist, and occasionally one attendant, represented the paternal side. As a development of his adjustment to these parental surrogates, the child tries to reestablish his human environment. During this vital period the psychiatric teamwork of the persons in charge has to withstand the crucial test. In order to prevent and handle the ensuing difficulties, much work has to be done with the various persons who work with the children. Daily conferences are held, in which all therapeutists participate. The therapeutic value of these discussions cannot be overestimated. Only persons definitely endowed with understanding of children's problems, as well as with a great amount of warmth and affection for children, can persist in this trying type of work.

BARBOUR, Peoria, Ill.

Diseases of the Ductless Glands; Endocrinology

DIETS FOR CHILDREN WITH DIABETES MELLITUS. ENRICO COMOLLI, Pediatria **54**:405, 1946.

The author asserts that actually there is no specific alimentary regimen for treatment of diabetes in children.

While admitting the necessity for meeting the nutritional requirements for growth in diabetic children, various authors generally advise insufficient diets.

The author, on the basis of the nutritional values fixed for children, suggests a scheme of treatment with diet and insulin for children with diabetes.

FROM THE AUTHOR'S SUMMARY.

ENLARGEMENT OF THE THYROID GLAND IN CHILDHOOD. P. WINOCUR and E. ROSEMBERG, Arch. argent. de pediat. **26**:39 (July) 1946.

The work is based on the study of 36 children: 11 boys, aged 6 to 11 years, and 25 girls, aged 6 to 16 years. A brief review of the etiopathogenic factors in goiter is given.

Size.—Only 3 boys and 9 girls presented enlargement of the thyroid gland. The rest showed a visible gland; but all were thin children, and for this reason the enlargement is questionable.

Heritage.—Fifty per cent reported a family history of goiter. This percentage must be higher, since enlargement of the thyroid, overlooked by the relatives, was sometimes found in the mother or 1 of the siblings.

Sex.—The incidence was higher in girls.

Race.—There was a relative predominance of Syrolebanese and Armenians in this series.

Development.—The body length was usually greater than usual. Ossification (roentgenograms of wrists and hands) did not appear delayed; on the contrary, it was advanced in some cases.

Clinical Picture.—Clinical examination did not disclose symptoms of disturbances of the thyroid. The mental condition was normal in all cases. The cholesterol content of the blood (determined by Schoenheimer and Sperry's method) was high as a rule. In 12 cases values were above 150 mg. per hundred cubic centimeters. However, hypercholesteremia is of little aid in the diagnosis of hyperthyroidism.

ROJAS, Boston.

HYPOGLYCEMIA IN CHILDREN. FRITZ KARLSTROM, Svenska läk.-tidning. **42**:1916 (July 13) 1945.

The author reports 2 cases of hypoglycemia (lowest value for blood sugar, 40 and 57 mg. per hundred cubic centimeters, respectively) in newborn infants of diabetic mothers; 1 case of a spontaneous hypoglycemic attack with loss of consciousness (lowest value, 46 mg. per hundred cubic centimeters) in a 3 year old girl, and 1 case of repeated morning convulsions in a boy, aged 9½ years, with epilepsy (lowest value, 43 mg. per hundred cubic centimeters).

WALLGREN, Stockholm, Sweden.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

H. William Elghammer M.D., *President*

Regular Meeting, Feb. 17, 1948

Incidence of Sicklemia in the Newborn Negro Infant. Dr. Roland B. Scott, Dr. Robert P. Crawford and Dr. Melvin Jenkins, Washington, D. C.

This paper was published in full in the June 1948 issue of the American Journal of Diseases of Children.

DISCUSSION

Dr. H. William Elghammer: Do you have any figures on sedimentation rates, or on the relationship of sicklemia to rheumatic fever?

Dr. M. P. Borovsky: So far as I know, there has been no work on sicklemia at the Children's Division of Cook County Hospital, but I can recall a newborn infant who displayed umbilical bleeding which was thought to be due to hemorrhagic disease of the newborn. The condition did not respond to vitamin K but did respond to blood transfusion and, so far as I know, was one of the earliest cases that showed sickling. I believe a study there might show a similar percentage of sicklemia, but clinical manifestations were seen only in that one case so far as I can recall.

Dr. Roland B. Scott, Washington, D. C.: In regard to the relationship of the sedimentation rates in sickle cell anemia and rheumatic fever, there are several interesting possibilities in these two diseases which are sometimes confused. Ordinarily, the sedimentation rate is normal in each disease during the quiescent stage. The rapid sedimentation of the erythrocytes, commonly seen during the active acute stage of rheumatic fever, may also be observed during the crises in sickle cell anemia. These crises are often precipitated by acute intercurrent infections. I have observed that the increase in sedimentation rate of acute rheumatic fever may dramatically change to a low value should acute congestive cardiac failure ensue. This change in the sedimentation of the red cells in rheumatic heart disease with congestive failure is probably related to changes in the plasma proteins, particularly the globulin fraction. Severe anemic states are usually associated with acceleration of the sedimentation rate; however, cases of sickle cell anemia often present an exception to this rule. Some observers have expressed the opinion that the abnormal shape of the sickled cells prevents rouleau formation with resultant slowing of sedimentation. Winsor and Burch devised a diagnostic test for sickle cell anemia based on the slowing of the sedimentation of erythrocytes in this disease under the influence of carbon dioxide and acceleration of the rate by oxygen.

The case of bleeding from the umbilicus in the newborn is interesting. Perhaps an underlying infection served to activate a latent tendency to hemorrhage.

Treatment of Tuberculous Meningitis with Streptomycin. Dr. Abraham Levinson.

In the early part of 1947, my colleagues and I started treating the patients with tuberculous meningitis at the Children's Division of Cook County Hospital with

streptomycin. The results have been encouraging, although we observed that some patients who improved greatly, and who stayed well as long as several months, did have relapses. Our results are particularly interesting since practically all were treated intramuscularly; only 1 patient had intrathecal therapy for nine days.

In addition to study of the effect of streptomycin on the arrest of the disease, we investigated the changes in cerebrospinal fluid before, during and after streptomycin therapy, the streptomycin levels in the blood and cerebrospinal fluid, the blood picture at various stages of the disease and the accompanying pulmonary and other pathologic changes in the body. By prolonging the life of the patient streptomycin has indeed opened a new avenue of study in the pathogenesis, pathology and symptomatology of tuberculous meningitis.

To date, we have treated 19 patients with streptomycin; 8 are alive and improved, and 11 died. In the patients who showed improvement, the immediate response to streptomycin was striking. Improvement occurred in a few days and the temperature subsided, in spite of the fact that the cerebrospinal fluid and roentgenograms still showed pathologic changes.

The dosage of streptomycin was 200,000 units every three hours for ninety days. We believe that in time we will be able to cut down dosage and length of treatment. At present, however, we have given all the patients the same dose. In 2 patients there was deafness but, since any meningitis may result in deafness, the reduced hearing ability may not have been due to streptomycin. Furthermore, in 1 patient there was a history of deafness for four days prior to admission. The data on streptomycin levels are as yet too meager, but we obtained levels of 40 to 160 micrograms in some patients, which is significant. We learned that the cerebrospinal fluid takes up streptomycin when it is injected intramuscularly.

The cerebrospinal fluid changes during streptomycin treatment are illuminating. It takes three to four months before the cells and the protein return to normal. The glucose concentration, which is reduced in all patients with tuberculous meningitis, rises to normal, sometimes within a few days. The reaction to the Levinson test stays positive for two to three months. In patients who do well, the reaction to the test becomes negative; in those who do not improve the reaction remains positive. The chlorides usually remain reduced for three to four months, until there is definite improvement. The chlorides, however, are not a reliable guide to recovery, but are rather an index to the state of general dehydration.

The roentgenograms of the chest showed pulmonary pathologic lesions in 17 of the patients. In most, pulmonary changes subsided parallel to the subsidence of the meningitis. In 1 patient, the pulmonary pathologic lesions persisted even after the meningeal symptoms disappeared.

It is still too early to state that patients with tuberculous meningitis recover under streptomycin therapy. All one can say is that there is definite arrest of the disease. However, in view of the hopelessness of the disease with other forms of treatment, all patients with tuberculous meningitis should be treated with streptomycin.

DISCUSSION

DR. LOUIS C. MORRIS: I am not a pediatrician and my experience with streptomycin therapy in tuberculosis is that of active participation in the program at the Veterans Administration Facility, Hines, Ill. I shall attempt to discuss some of the salient effects of this antibiotic substance in tuberculous meningoencephalitis in relation to the work of Dr. Levinson.

I think it is generally accepted by most pathologists and by many clinicians—although there is not universal agreement—that tuberculous meningitis does not develop directly from the seeding of the meninges by the blood stream. The

accepted opinion, following the contention of Rich and McCordock and others, is that the initial lesions in central nervous system involvement by tuberculosis are, generally speaking, tuberculomas in the cerebral substance or meninges, and that tuberculous meningitis develops from these either directly into the subarachnoid-cisternal and ventricular spaces from superficial cerebral or meningeal foci, or through the Virchow-Robin spaces from deeply placed foci. These precursor tuberculomas may be single or multiple and, in order to demonstrate them clearly—for some of them are not grossly discernible—brain sections as fine as 2 mm. in thickness must be made. I know that Dr. Levinson takes exception to this view and belongs to the group that states its belief in the direct hematogenous seeding of the meninges. The evidence, however, is steadily mounting in favor of the observations of Rich and McCordock. The recent excellent investigation of Dr. J. Schwarz, of Chile (*Am. Rev. Tuberc.* **57**:63 [Jan.] 1948), offers such corroborative evidence.

Furthermore, these preliminary cerebral and meningeal tuberculomas are usually older than the more recent miliary lesions seen on the meningeal surface and elsewhere in the body. In only about 50 per cent of the patients with miliary tuberculosis does meningitis manifest itself; whereas in patients with meningitis miliary lesions are present elsewhere in the body in 70 per cent or more. Finally, the observation in patients with miliary-meningeal tuberculosis who are treated with streptomycin, that there is clearing of the miliary lesions in the lungs while the tuberculosis progresses in the central nervous system, tends indirectly to substantiate the views mentioned.

If this is true, and the weight of evidence is in this direction, treatment of tuberculous meningoencephalitis should be directed both toward prevention of cerebral and meningeal tuberculomas and toward eradication of the tuberculous meningitis specifically. It is claimed that tuberculous seeding of distant organs, other than those involved by primary tuberculosis, such as the bones, genitourinary organs and brain, takes place during or shortly after the appearance of primary tuberculosis (Lincoln and others). Of course, this situation is more frequently encountered in persons of younger age groups, in whom both primary and distant lesions are predominantly benign. In adults, hematogenous miliary seedings are occasionally seen after surgical procedures on the osseous and other systems, and in about 5 per cent of those who died with far advanced pulmonary tuberculosis. These hematogenous seedings are predominantly fatal. In a small percentage of primary tuberculosis, progression occurs with miliary-meningeal involvement.

Most of the cases in Dr. Levinson's series are apparently instances of tuberculous meningoencephalitis in the course of progressive primary pulmonary tuberculosis in infants and young children. This is one reason that his results are so much better than those with adults. Our immediate results demonstrated a reversal of the meningeal process which, however, was almost invariably only temporary; even after more than one reversal the ultimate outcome was fatal in practically all cases. In Dr. Levinson's series treatment was instituted during the early dissemination of the tubercle bacillus. Thus, he was able to attack the earliest lesions in the brain and the meninges with streptomycin, before they became stabilized as characteristic tuberculomas. Lesions such as the typical caseofibrocalciferous tuberculous nodules cannot be much influenced by the antibiotic substance because it cannot penetrate them.

The challenge of tuberculous meningitis, so far as pediatricians are concerned, can be met. Periodic tuberculin tests in groups most likely to develop primary tuberculosis should serve to detect the disease at the earliest possible time. Primary tuberculosis should be attacked and overcome by specific therapy such as strepto-

mycin not only because the usual benign course of the primary disease may be shortened but also because specific therapy at this stage may prevent establishment of distant foci in the bones and other organs. The reactivation of such latent foci later in life, long after the primary lesion has healed, produces isolated organ tuberculosis unless they are rendered impotent at the start.

The dosage employed by Dr. Levinson is far greater in proportion to body weight than we have used in adults (2 Gm. intramuscularly and 0.05 Gm. intrathecally every other day). We are in agreement with him in not favoring the intrathecal administration of drugs. However, our treatment procedure is based on the early work of Hinshaw, who demonstrated better results in those patients treated by the combined routes.

Streptomycin is toxic, especially to the nucleus of the eighth nerve, when administered in high dosage. We observed that the impurities which were present at first had nothing to do with this nerve involvement; it was entirely a matter of dosage. With a daily dose of 2 Gm. the incidence of involvement of the eighth nerve, and specifically destruction of vestibular function, was 96 per cent; with 1 Gm. dosage this was reduced to 23 per cent and with 0.5 Gm. dosage the incidence was still further reduced. Loss of vestibular function appears usually after the drug has been given for three to four weeks. The impairment cannot always be detected by subjective signs, but it can readily be ascertained by blindfolding the patient and observing his gait along a directed straight course. The damage can be accurately determined only by specific otologic tests, which should be performed on all patients receiving streptomycin therapy. Loss of hearing is infrequent and has occurred in less than 2 per cent of more than 1,000 patients treated. Hearing loss is reversible if detected early; vestibular loss, although compensated for by the cerebellum, may be permanent.

With a 2 Gm. daily intramuscular dose in adults, the streptomycin level in the spinal fluid usually exceeded the 0.5 to 1.5 micrograms per cubic centimeter said to be effective in inhibiting the multiplication of the tubercle bacillus in vitro by as much as four times. The dosage given by Dr. Levinson is from four to ten times that we have given, in proportion to weight. He has reported no results of otologic tests.

I should like to answer some of the questions raised by Dr. Levinson. The first is that of the rapid rise of the depressed spinal fluid glucose level following the initiation of streptomycin therapy. One should know what method is used to determine "glucose" values—specific "glucose" methods or methods to determine "reducing substances." Glucose is a nutrient substance for the tubercle bacilli, and any agent that will inhibit their multiplication will of necessity spare glucose. It is also known that streptomycin elaborates a "reducing" substance. In his cases the streptomycin levels were quite high in the spinal fluid. The second question—the persistence of tubercle bacilli in the spinal fluid in the face of clinical improvement, even to arrest—may indicate the persistence of organisms resistant to streptomycin yet with attenuated virulence.

I should like to present two ideas in closing. The first concerns the relation of the central nervous system vascular supply. Batson described the vertebral system of veins, an extensive intercommunicating valveless system that anastomoses on the one hand with the cerebral veins and on the other with the somatic veins of the torso. The occurrence of cerebral metastases from lesions and, in particular, from neoplastic ones in the pelvis, without obvious passage through the lungs has been explained by the reference to this system of vertebral veins. Might it not be possible to reach higher levels in the cerebrospinal fluid by injection of drugs into the vertebral system of veins so as to by-pass the lungs?

The second thought deals with the postulation of a mechanical factor in tuberculous meningitis that may play a major role in hastening death in this disease. Many of those afflicted with this disease die with internal hydrocephalus, apparently brought on by blocking of the many small apertures in the cisternal fluid ways of the central nervous system, by matting of tissues caused by deposition of fibrin. In tuberculous infections there is considerable outpouring of fibrinogen into the spinal fluid, and this is soon converted into fibrin and its adhesive successors. Might not the use of some anticoagulant such as heparin, simultaneously with the chemotherapeutic agent, maintain a free flow in the spinal fluid ways and insure better action of the specific drug?

DR. ARCHIBALD L. HOYNE: About fourteen years ago my associates and I abandoned intrathecal therapy for meningococcic meningitis, and shortly afterward gave up the long-established custom in respect to that form of treatment for all forms of meningitis. I have always felt that Dr. Levinson was not fully in accord with our opinions regarding therapy. But in view of the remarkable results he has presented and his splendid discussion, I should like to inquire whether he is now convinced that a patient can make a good recovery without intrathecal therapy.

Adrenogenital Syndrome in Children. DR. MATTHEW M. STEINER and DR. K. E. BARBER.

The adrenogenital syndrome is a condition characterized by sexual precocity resulting from a disturbance of the adrenal cortex, due to hyperfunction, hyperplasia or neoplasm. It has been shown that the adrenal cortex elaborates both male and female sex hormones (androgens and estrogens), as well as other steroids. However, the clinical expression of the adrenogenital syndrome is conditioned not alone by the nature of the hormones elaborated during a disturbance of the adrenal cortex, but also by the age and sex of the patient, so that one is confronted with a variety of signs and symptoms depending on these three factors in general. This accounts for the heterogenicity of the adrenogenital syndrome.

CASE 1.—A white girl, aged 3 years 2 months, was admitted to the hospital because of enlargement of the clitoris and growth of pubic hair. Physical examination revealed: height 42 inches (107 cm.) (average for children aged 4½ years), acne and comedos of face, huskiness of voice, adult distribution of pubic hair and enlarged labia majora. The clitoris projected ½ inch (1.3 cm.) from between the labia minora, which surrounded it in cowl-like fashion. The blood pressure was elevated; the sella turcica was normal. There were eight carpal centers in the wrist (skeletal age about 11 years). Intravenous pyelograms and perirenal air insufflation studies gave normal results. The urinary excretion of 17-ketosteroids was 9 mg. and of pregnandiol, 6 mg. per twenty-four hours. Laparotomy revealed a normal uterus, fallopian tubes and ovaries. Microscopic examination of the left adrenal gland showed "hyperplasia of the adrenal cortex." Later, the right adrenal was removed and similar changes were noted within the cortex.

CASE 2.—An 18 month old white child was admitted to the hospital because of growth of pubic hair and enlargement of a phallus. At the time of birth the infant was considered to be female. At the age of 9 months it was decided to rear the child as a male because of the growth of a "penis," although complete hypospadias was present and no testes were palpated. Physical examination showed the height to be 36 inches (91 cm.) (average for children aged 2½ years), acne and comedos of face, adult distribution of pubic hair and a phallus measuring 1½ inches (3.8 cm.) in length and ¾ inch (1.9 cm.) in width, partly covered by a prepuce and containing no urethral orifice. At the base of the phallus an orifice led into the bladder, through which urination occurred. No testes or internal

genitalia were palpable. There were seven carpal centers in the wrist (skeletal age about 8 years). Intravenous pyelograms were normal. Urinary excretion of 17-ketosteroids was 17.5 mg. and of pregnandiol, 37.1 mg. per twenty-four hours.

Laparotomy revealed an underdeveloped uterus, strandlike fallopian tubes and two minute ovaries. The left adrenal gland appeared enlarged and was removed. Microscopic section revealed "hyperplasia of the adrenal cortex."

DISCUSSION

DR. K. E. BARBER: I think the second patient is interesting from a urologic standpoint. I thought this child was a male with a hypospadias and undescended testes. The phallus, glans and shaft seemed normal, even to the hooded foreskin that is present with a penile type of hypospadias. The scrotal tissue was wrinkled and appeared normal except for size. The testes could be located in neither the scrotum nor the inguinal canals, nor by rectal examination. No prostatic tissue was definitely palpable, but some thickening was felt. One had the impression that this was a case of bilateral abdominal testes. Since the pregnandiol in the urine was 37.1 mg. per twenty-four hours, Dr. Steiner remarked that some ovarian tissue must be present. The mother wants this child to be a boy, and, since no true or false vagina was found, an attempt will be made to repair the hypospadias, then the ovaries and uterus will be removed. This case proves to me that exploratory laparotomy must be done in such cases to see whether ovarian or testicular tissue, or both, is present.

The first case was not a real urologic problem except from the angle of adrenal hyperplasia. Perirenal insufflation was done to see whether a tumor or enlargement of the adrenals could be demonstrated. One hundred cubic centimeters of air was injected into the right perirenal area; then roentgenograms were taken over a period of six hours. Three days later the same procedure was done on the left side. Good roentgenograms which outlined the adrenal glands and showed no enlargement or tumor were obtained. A laparotomy was then performed to determine the presence of any supernumerary adrenals, and also for examination of the uterus, tubes and ovaries. Two pieces of tissue were removed from each ovary for biopsy. The adrenals were palpated and found to be about normal size. A piece of adrenal tissue was removed from the left adrenal gland for microscopic study. Later, an adrenalectomy (right side) was done. This is not a difficult procedure in a child. The adrenal gland usually can be brought down with the kidney. The problem in this child is: Should the enlarged clitoris or a part of the source of stimulation be removed? Time will tell.

DR. HENRY S. GUTERMAN: Surgical intervention is the most favorable therapeutic approach to these cases. Before this approach is attempted, precautions must be taken to establish the presence of both adrenal glands. Perirenal air insufflation may give satisfactory roentgenographic visualization of the adrenals. If the results are not clear, then both adrenal areas should be exposed at operation to determine the presence of the organs bilaterally.

Surgical treatment involving the adrenal gland may be associated with shock and acute adrenocortical insufficiency. In the laboratory I have observed that these untoward symptoms may be alleviated by infiltration of the entire periadrenal area with procaine hydrochloride U. S. P. ("novocaine") prior to manipulation and excision of the gland. This procedure was followed in the cases reported by Dr. Steiner and Dr. Barber. It should be stated that when both adrenals are hyperplastic and one is removed the remaining gland usually can maintain the endocrine secretory functions necessary for life. Signs of adrenal insufficiency may not appear in such cases in the postoperative period. When a unilateral adenoma or

tumor is the disturbing cause, excision may be followed by the alarming symptoms of adrenal cortical insufficiency (addisonian crisis). This is particularly true when the involved adrenal is producing the "metabolic steroids" (Cushing's syndrome); the contralateral gland is usually hypotrophic.

For these patients I advocate the use of potent adrenocortical extracts in the postoperative period (the amount and frequency determined by the blood pressure and pulse) until the remaining gland can resume normal function.

The precautions of (1) verification of the presence of both adrenal glands, (2) infiltration of the adrenal area before manipulation and excision and (3) the postoperative use of adrenal extracts in adequate amounts should help assure the recovery of more patients undergoing surgical treatment of the adrenal gland.

SOCIETY FOR PEDIATRIC RESEARCH

Mitchell I. Rubin, M.D., *President*

Seventeenth Annual Meeting, Stockbridge, Mass., May 12-13, 1947

First Session

Monday Afternoon, May 12

Presidential Address. DR. MITCHELL I. RUBIN, Buffalo.

Electrolyte Studies in Nephrosis: Induction of Diuresis by Administration of Salts of Sodium and Potassium. DR. CHARLES L. FOX JR. and DR. DONOVAN J. MCCUNE, New York.

Reduction in plasma sodium and acidosis move water into cells (Peters, Gamble), impairing renal excretion of water. Correction of the low plasma sodium and bicarbonate levels occurring in nephrosis might be expected to move water out of swollen cells and permit its excretion.

Accordingly, children with nephrosis were given sodium lactate or acetate in amounts sufficient to produce high values of plasma sodium and bicarbonate. Because pronounced potassiuria had been observed while edema was forming, potassium acetate was administered simultaneously and in amounts nearly equivalent to the sodium salts.

Initially, body weight rose 2 per cent. The volume of urine increased, and its sodium concentration exceeded 250 milliequivalents per liter. Treatment was interrupted when the plasma sodium became stabilized at more than 150 milliequivalents per liter. The concentration of sodium in the urine then receded to 155 milliequivalents per liter; chloride increased rapidly to the plasma level, and renal osmotic work became minimal. Diuresis occurred, and edema and ascites disappeared.

Balance studies recovered the amount of sodium calculated from intake plus loss of edema fluid. However, an unpredictable surplus excretion of chloride exceeded the excretion of sodium by about 45 milliequivalents per kilogram of body weight. Significantly, the chloride concentration of the erythrocytes before diuresis exceeded normal by that amount; likewise, the volume of distribution of radiobromide, a measure of the distribution of halide, exceeded that of radiosodium.

The changes in plasma and urine electrolytes during spontaneous diuresis were similar to those in 6 children who had diuresis after therapy.

There is some evidence that maintenance therapy directed at reducing renal osmotic work may result in protracted remission.

Aminoaciduria in Fanconi Syndrome (Tubular Renal Rickets). DR. C. E. DENT, London, England.

The urine in 3 cases of the Fanconi syndrome (tubular renal rickets), all with cirrhosis of the liver, was studied with special reference to the amino acids present. The new technic of partition chromatography using filter paper was applied, together with more conventional methods. These urines resembled each other closely in amino acid distribution. Most of the results quoted, however, are from one of the cases more fully studied.

The aminoaciduria was followed for seven months, daily analyses being made during the six weeks before death from hepatic failure. The total twenty-four hour output of aminonitrogen varied from 500 to 1,650 mg. (normal value, 100 to 400 mg.). This is equivalent to 5 to 16 Gm. of amino acids. The ratio (amino nitrogen/total nitrogen) × 100 was 4:12 (normal 1:2). The daily variations occurred spontaneously and were not related to dietary intake of protein or to the clinical condition. However, a large output always occurred when there was a spontaneous diuresis leading to a negative fluid balance. Conversely, low outputs occurred on days in which fluid was retained. There was no simple relation to the total volume of urine.

All the amino acids commonly found in proteins were detected in the urine, except lysine and tryptophane. Methionine and cystine occurred in normal quantities, the others in larger amounts than usual. Two rare amino acids were also detected, citrulline and amino-n-butyric acid. There was also evidence of a peptide containing serine and glycine, of traces of taurine and of complexes which liberated asparaginic and glutamic acids on hydrolysis. The pattern of excretion of the amino acids was remarkably constant from day to day and was not altered by widely different diets, blood transfusions, or by changes in the clinical condition of the patient. The pattern bore no resemblance to the hydrolysis of a typical food protein such as casein.

The mechanism of the excretion of amino acids was shown to be renal in type, i. e., it occurred in the presence of a normal blood level of aminonitrogen. This confirmed the suggestion originally made by Fanconi. The twenty-four hour output of glucose varied from 4 to 23 Gm. The amount of glucose excreted varied directly with the amount of aminonitrogen according to a straight-line relationship. It is interesting to speculate on whether this relationship would also hold during the increased glucose output after ingestion of sugar. If so, there is a possibility that the coma twice reported to occur in these patients during dextrose tolerance tests might be connected with the forced excretion of amino acids and the consequent temporary lowering of the blood level. The renal aminoaciduria of these patients provides a valuable opportunity to investigate problems of amino acid metabolism. For instance, after administration of methionine, excretion of amino-n-butyric acid in the urine is increased as though it were formed by breakdown of the methionine. The high renal threshold in the normal person serves to mask such changes in urinary distribution of amino acids.

The cause of the bone disease is not yet certain. The chronic acidosis may be absent throughout the course of the disease. The low level of inorganic phosphate in the blood may occur only in the later stages after the bony changes are well developed. Hence the two most likely causes cannot be definitely incriminated. Are bony changes the result of excessive and chronic loss of amino acids in the urine?

Clinical Evaluation of Caronamide for Competitive Inhibition of Penicillin Excretion. Dr. Milton Rapoport, Dr. F. Bruce Corneal, Dr. Karl H. Beyer and Dr. W. F. Verwey, Philadelphia.

In animals Beyer demonstrated that caronamide (4-carboxy-phenylmethanesulfonanilide), by inhibiting the rapid renal excretion of penicillin, was capable of maintaining higher and more sustained plasma levels of the antibiotic substance than normally occurred after a given dose. In this paper is presented an evaluation of the dosage and toxicity of this compound in children and of its efficacy in increasing and sustaining the plasma concentration of orally administered penicillin.

Improved Flame Photometer for Sodium and Potassium Analyses. Dr. William M. Wallace, Boston.

Berry, Chappell and Barnes recently described an improved type of flame photometer for the analysis of sodium and potassium which overcame the objectionable features of the earlier models. The instrument described in this paper was constructed along lines found successful by Dr. Charles L. Fox. The present model employs a dual optical system with lithium as an internal standard element. The latter is added in constant amount to all standards and unknowns. Liquid unknowns are vaporized in a specially constructed chamber and the vapors drawn into a constantly regulated gas flame. The particles of unknown and standard are heated to incandescence to emit their characteristic wavelengths. By means of paired apertures in the burner chimney, twin beams of light are passed through light filters selectively transmitting the unknown and standard wavelengths. The beams are then focused on two photoelectric cells, so connected that the generated currents oppose one another through a galvanometer. The latter functions as a null point indicator. The amount of current drawn from the standard cell is varied to balance the unknown cell by means of a potentiometer resistance. Thus, the ratio of unknown to standard is measured rather than the absolute light intensities. This teature cancels out minor variations in the operation of the flame and atomizer, as well as the interference of foreign molecules. In practice the instrument is calibrated against standards.

Liquid biologic material is analyzed by simple dilution with water after addition of the standard amount of lithium. Dilutions of the order of 1:50 to 1:200 are most convenient. Stools, diets and tissues may be analyzed after dry or wet ashing. An alternative, more rapid and economical preparation can be made by the use of nitric acid filtrates. The semisolid material is homogenized in a Waring blendor and aliquots pipetted into volumetric flasks. The aliquots are then diluted to volume with tenth-normal nitric acid and filtered. Such filtrates appear to contain all the base as well as the chloride of the material. The ratio of wet solid to volume of filtrate must be kept larger than 1:20 so that the volume effect of the solids on the filtrate concentration will lie within the margin for error of the method. Such filtrates are ideal for flame photometry by virtue of their great dilution but are too cumbersome for chemical determination.

Serum sodium in 0.1 cc. can be determined with an outside accuracy of 2 per cent and serum potassium in 1.0 cc. with an accuracy of 5 per cent. Urine, diets, stools and tissues can be analyzed on single determinations with an average error of 1 per cent and an extreme error of 2 per cent. If duplicate determinations at different dilutions are employed, the degree of accuracy can be greatly improved.

The method lends itself particularly to metabolic studies because of its rapidity and economy. Measurements may be completed by the end of a metabolic period and the experiment directed from period to period.

Treatment of Diarrhea with Potassium and Sodium Salts. Dr. J. Flett Jr., Dr. E. L. Pratt and Dr. D. C. Darrow, New Haven, Conn.

A method of treating infantile diarrhea with potassium as well as sodium salts and the results of this treatment in 80 infants are discussed.

The children were divided into three groups—the severely sick, the moderately sick and the mildly sick patients. The distinction was made on the basis of (1) clinical impression of severity and (2) the serum bicarbonate level. A level of 15 milliequivalents or less was considered to represent a severely sick infant.

The greatest incidence of the disease was in the children less than 3 months of age, and 88 per cent of all the severe cases occurred in children who were less than 6 months of age.

Treatment consisted of administration of plasma or blood and isotonic sodium chloride solution, the replacement of water and electrolyte, including potassium, the early institution of oral intake of water and electrolyte, the gradual increase of caloric intake and the inclusion of potassium in all feeding mixtures that contained less than 80 calories per kilogram of body weight.

Plasma and saline solution were given intravenously and averaged 30 cc. per kilogram of body weight. Potassium lactate solution was given subcutaneously by slow drip clysis and averaged between 60 and 80 cc. per kilogram. Five or 10 per cent solution of glucose was given intravenously to supply the remaining water deficit. Total volume of fluid given during the first day averaged nearly 200 cc. per kilogram of body weight for the severely sick infants and 180 cc. per kilogram of body weight for the moderately and mildly sick patients. Some of the severely sick babies were given a mixture of 1 part potassium lactate to 2 parts 5 per cent glucose solution orally on the day of admission, and 75 per cent of them began to take this mixture on the second day. Many more of the moderately and mildly sick babies were able to take it on the first day. Caloric intake was slowly increased, and 1 Gm. of potassium chloride was added to all milk mixtures of less than 80 calories per kilogram of body weight.

Relapses occurred in 10 per cent of the patients and may have been due to (1) preexisting malnutrition, (2) too rapid an increase in caloric intake or (3) insufficient intake of fluids during treatment.

The mortality in this series was 5 per cent.

The return of serum bicarbonate and chloride values to the normal range by the third day of treatment is discussed.

Hyperosmolarity and Hyperelectrolytemia in Pathologic Conditions of Childhood. Dr. S. Rapoport, Cincinnati.

This paper was published in full in the December 1947 issue of the American Journal of Diseases of Children.

Pulmonary Stenosis or Atresia: Report on the First 300 Operations. Dr. Ruth Whittemore and Dr. Helen B. Taussig, Baltimore.

Of the first 300 patients operated on for pulmonary stenosis or atresia, 228 were discharged improved. Approximately 10 per cent of these patients were operated on two or more years ago and 90 per cent from six to eighteen months ago. This report is primarily concerned with the postoperative changes in the red blood cell count, hematocrit readings, arterial oxygen saturations and in the size of the heart of these patients.

By the time the patient left the hospital, his lips were of normal color and his tolerance for exercise greatly increased. The arterial oxygen saturation had risen

usually to 75 to 85 per cent. The red blood cell count, hemoglobin concentration and hematocrit reading had declined to normal levels. Studies at six month, one year and two year intervals showed this improvement was maintained in all but 2 instances; 1 child showed a fall in oxygen saturation and 1 a rise in red blood cell count.

Fifty-nine per cent of the patients had some cardiac enlargement prior to operation. Changes in heart size were studied by serial teleroentgenograms on 123 patients. No change in cardiac size was shown by 38.7 per cent; 41.9 per cent showed enlargement immediately after operation; 12.3 per cent showed an increase during the first six months after operation and 7.1 per cent not until one year later. Of the entire series, only 2 patients showed progressive cardiac enlargement. In all other instances, after the initial enlargement there was no further increase in the size of the heart.

Since discharge, 8 patients have died: 4 children and 4 infants. Severe cardiac decompensation developed in 2 children. Cyanosis recurred in 2 others. One child had subacute bacterial endocarditis and recovered. Of the entire group of patients there were only 7 from whom we have not heard. Thus, of the 228 patients discharged improved, 208 are known to be doing well.

Arterial Anoxemia in Noncyanotic Congenital Cardiac Disease. DR. NELSON K. ORDWAY, New Haven, Conn.

Formulas are described which make it possible to calculate in a quantitative manner the two factors which cause arterial oxygen unsaturation, even when both factors are operating simultaneously. These factors are "A," the right to left shunts of blood directly into the arterial circulation from the venous side, and "l," deficient oxygenation of the blood in the lungs. These calculations were applied to 5 children who were clinically free of cyanosis, but who had arterial oxygen saturations lying between 79 and 90 per cent. In 3 children in whom the l factor was increased, there was evidence of increased blood flow and/or increased pressure in the pulmonary circulation, produced by a left to right shunt or increased right ventricular pressure. A revision of Abbott's classification of congenital heart disease, based on an assessment of the A and l factors rather than on the presence or absence of cyanosis, is suggested.

Relationship of Hyaluronidase to Rheumatic Fever. DR. ALBERT DORFMAN, DR. MELVIN OTT and DR. ELIZABETH J. REIMERS, Chicago.

The widespread existence of an enzyme (hyaluronidase) which hydrolyzes hyaluronic acid, a component of connective tissue, has been long recognized. Recent reports of the ability of salicylates to inhibit this enzyme and of the existence of an inhibitor of this enzyme in human blood focused attention on the relationship of hyaluronidase to diseases of the connective tissue.

Studies on the in vivo inhibition by salicylates of the spreading activity of hyaluronidase confirmed the previous results of Guerra. Salicylates were also observed to inhibit the activity of hyaluronidase prepared from bull testes and filtrates of Clostridium perfringens when tested by both the viscosity and the chemical methods. The concentrations of salicylates necessary for the in vitro effect are considerably greater than those required for the in vivo inhibition of spreading activity, indicating that the explanation of these phenomena may be more complex than the direct action of salicylates on hyaluronidase.

Studies on the hyaluronidase (testicular) inhibitor in human blood indicate that its concentration varies with age and sex.

The production of rheumatic symptoms by streptococcus hyaluronidase is open to two serious objections: (*a*) rheumatic symptoms do not coincide with the streptococcus infection, and (*b*) most group A streptococci do not produce hyaluronidase.

It is suggested that the breakup of connective tissue may be caused by hyaluronidase produced by the subject as a result of exposure to hyaluronic acid in the capsule of the streptococcus. The development of rheumatic symptoms may then depend on variations in concentration of inhibitor.

Second Session

Tuesday Morning, May 13

Treatment of Hypoglycemic Convulsions with Alloxan. DR. NATHAN B. TALBOT, DR. JOHN CRAWFORD and DR. CABELL C. BAILEY, Boston.

The patient was an 8 month old girl who had had intermittent episodes of disorientation, twitching of facial muscles and convulsions of three months' duration. The cause of these complaints was pronounced hypoglycemia. Extensive studies appeared to indicate that the hypoglycemia was due to hyperinsulinism rather than to hepatic disease, galactosemia, hypoadrenocorticism or the like. At exploratory laparotomy no pancreatic islet tumor could be seen. However, rather than perform a partial pancreatectomy, it was decided to administer alloxan, which in certain animals is known to destroy insulin-producing pancreatic cells. The patient was given two courses of therapy. During both periods of alloxan administration, blood sugar values rose to normal levels and the symptoms of hypoglycemia disappeared. After the first course of therapy, the hypoglycemia and symptoms recurred, but no hypoglycemia has occurred following the second course. No toxic manifestations were noted. Though convulsions associated with hypoglycemia have also ceased, the patient has had occasional convulsions during periods of fever. Pneumoencephalograms obtained several weeks after the last hypoglycemic episode revealed considerable internal hydrocephalus and cortical atrophy. A series of electroencephalograms suggested that the damage to the brain was minimal or absent early in the disease and that it may have developed as a result of the hypoglycemia. It is concluded that alloxan is worthy of further study in this type of patient.

Iron Absorption in Premature and Full Term Infants. DR. LEON OETTINGER JR., DR. WILLARD B. MILLS and DR. PAUL F. HAHN, Nashville, Tenn.

A reliable method for the determination of the amount of iron absorbed from the gastrointestinal tract has long been needed in order better to study the anemia of premature and full term infants. This has become necessary because of the tedious and inherently inaccurate methods used in iron balance studies, the unreliability of plasma iron level as a measurement of absorption alone and the difficulties in evaluation of iron absorption from secondary responses such as those of the red blood cells, the reticulocytes and the hemoglobin content when they are subject to other factors as well.

In the present study, radioactive or "tagged" iron was used in an attempt to determine whether or not premature and full term infants had an adequate iron store at birth and whether or not the mechanism for the absorption of iron is present and functioning at birth in both groups.

Tagged iron was first used in 1938 because of the possibility of detecting it even in concentrations of millimicrograms and of separating it from the natural iron already present in the body.

In normal persons about 1 to 7 per cent of a single test dose of 20 to 30 mg. of tagged iron given orally is absorbed, while in persons with iron deficiency anemias 15 to 60 per cent of a single test dose is absorbed. Pregnant women absorbed from 18 per cent in the first quarter to 36 per cent in the fourth quarter of pregnancy.

It has, therefore, been concluded from these and other studies that iron absorption from the gastrointestinal tract is proportional to need and that the normal range of absorption is 1 to 10 per cent, while in cases of increased demand the range is from 15 to 16 per cent.

In the present study, 10 premature and 14 full term infants were given single test doses of tagged iron and the amount absorbed was determined by the method of Hahn.

It was found that the premature group absorbed from 0.2 to 7.0 per cent of the test dose, while full term infants absorbed from 0.4 to 8.0 per cent. The arithmetic means of the two groups were 2.8 per cent for the premature infants and 3.2 per cent for the full term infants. This difference is not statistically significant.

When the amount of iron absorbed was plotted against the maternal hemoglobin concentration, no correlation could be obtained for premature or full term infants.

From these results it could be concluded that both full term and premature infants had adequate iron stores at the time of birth, regardless of the maternal hemoglobin concentration, and that both premature and full term infants could absorb iron from the gastrointestinal tract at the time of birth.

Comparative Nutritive Value of Casein and of Lactalbumin for Man.

Dr. Warren M. Cox Jr., Dr. Arthur J. Mueller, Dr. Robert Elman, Dr. Anthony A. Albanese and Dr. L. Emmett Holt Jr., New York.

It is known that the addition of cystine or of methionine to casein improves the rate of growth of rats when this protein is fed at a low intake level. Lactalbumin is as effective as supplemented casein when administered at the same nitrogen intake level.

When similar supplementation experiments in man, using a casein hydrolysate, were attempted, there was no evidence of improved nitrogen retention. Four groups of human subjects were employed. In the first group, 3 patients with complete pyloric obstruction were given 2 liters of amigen 5 per cent in 5 per cent "dextrose solution" intravenously daily as the sole source of nourishment for five days. The addition of methionine for the next five day period did not improve nitrogen retention. Two infants were fed an enzymic casein hydrolysate with and without added quantities of methionine for periods of five days with no improvement in nitrogen retention when methionine was added. Ten adult volunteers were divided into two groups: one group was placed on a maintenance level of nitrogen and showed no improvement in nitrogen retention when cystine was added to the casein hydrolysate. The other group was given no protein for twenty-one days, and casein hydrolysate sufficient only to equal the endogenous loss was added to the daily intake for five days. The addition of methionine did not improve retention.

These observations were extended to include a comparison of an additional 4 adult volunteers who were depleted of protein for twelve days, with subsequent administration of intact casein and intact lactalbumin for two periods of four days each. Each period of protein feeding was interspersed with a four day depletion period. A low level of protein supplementation (0.033 Gm. nitrogen per kilogram per day) was chosen in order to secure maximum utilization. The average nitrogen balances for the separate periods were: for casein, —0.79 and —0.68 Gm. daily, and for lactalbumin, —0.80 and —0.71 Gm. daily. The calculated biologic values for casein were 89.0 and 94.7 Gm. and for lactalbumin, 90.2 and 93.3 Gm.

These data indicate that the human requirement for the sulfur-containing amino acids is less than that of the rat and dog. It is possible that this difference is based on the fact that the rat and dog are covered with hair and man is not. Whether this explanation is true or not, it can be concluded that lactalbumin and casein are equally effective for nitrogen maintenance in man.

Carbonic Anhydrase in the Blood and Kidneys of Premature Infants. Dr. Richard L. Day and Dr. R. Martin Du Pan, New York.

Stevenson showed that the blood level of carbonic anhydrase is low in premature infants, and he attributed respiratory difficulties to this. Hober showed that the carbonic anhydrase in the kidney is essential in the acidification of urine. We observed that, though the blood level (in 31 cases) of carbonic anhydrase is indeed low in premature infants, there is no correlation of its level with oxygen saturation or carbon dioxide content. Autopsy specimens from 4 premature infants showed substantial amounts of carbonic anhydrase in the renal cortex, and little or none in the medulla after allowance for contaminating blood. It is well known that premature infants can produce extremely acid urine.

Development of Resistance to Streptomycin. Dr. Henry K. Silver and Dr. C. Henry Kempe, San Francisco.

The development of resistance to streptomycin is of practical as well as theoretic importance since resistant strains of pathogenic organisms develop with relative frequency after treatment with the drug. Sensitivity tests on isolated individual components of a strain of Escherichia coli were done, using a test first described at the last meeting of the Society for Pediatric Research (Kempe, H. C., and Silver, H.: Chick Embryo Culture in the Diagnosis of Bacterial Infections and Streptomycin Sensitivity Tests, read before the Society for Pediatric Research, April 30, 1946, Am. J. Dis. Child. **73**:238-239 [Feb.] 1947). This test utilizes the fertile hen's egg as the culture medium.

Results substantiated the theory that even sensitive strains of an organism originally contain resistant components. The sensitivities of the individual components of any organism will form a curve of distribution if the results are plotted.

Suspensions of mixtures of colonies rather than of individual colonies should be used for streptomycin sensitivity tests to avoid the inadvertent testing of either extreme in the range and to determine the average sensitiveness of the strain tested.

Strains of micro-organisms could be made extremely resistant to streptomycin by being cultured on the chorioallantoic membrane of fertile eggs to which had been added constant subinhibitory amounts of streptomycin.

Specific Immunologic Tests in the Systemic Mycoses. Dr. David L. McVickar, Nashville, Tenn.

The recently advanced hypothesis that pulmonary calcification in persons with a negative reaction to tuberculin may be the representation of a benign mycotic systemic infection has made the development of specific immunologic tests for the mycoses an immediate necessity. For this purpose it will be necessary to explore the immunologic significance of the carbohydrate, protein and lipid fraction of each of the pathogenic fungi in question.

For such an investigation the fungi should preferably be grown in their in vivo form. With Coccidioides immitis this has not yet been found possible. But Histoplasma capsulatum can now be made to grow abundantly in the yeast phase, with

easily demonstrable capsule, on tryptose medium fortified with 5 per cent plasma. For culture vessels half-gallon Mason jars are used, with 150 cc. of medium. With heavy inoculums, maximal growth of the fungus will obtain within two to three weeks. With the use of a modification of a technic devised by Avery and Jolin in 1930, it was possible to comminute the organisms so thoroughly that the cellular contents were obtained in chemically unaltered state. The Avery-Jolin technic consists essentially of repeated percussion of the organism in an apparatus of simple design at the temperature of dry ice. After this procedure, the comminuted material is lyophilized, and the lipid components removed by extraction with ether and alcohol at —18 C. (—0.4 F.). The protein fractions are then extracted by successive leechings with increasingly alkaline buffer solutions. The polysaccharide portion may be obtained in extracts from which the protein has been precipitated, or more readily by fractional alcoholic precipitation of the broth filtrate, which has first been concentrated by vacuum distillation and dialysis.

With this technic, fractions have been obtained from each of the pathogenic fungi and are being subjected to further purification and to immunologic testing. Evidence is accumulating that fairly extensive cross reactions do exist.

Virus Synthesis. Dr. Seymour S. Cohen, Philadelphia.

The metabolism of Escherichia coli B infected with the bacterial virus, T_2r^+, was studied. Infected cells, which have the same rate of oxygen consumption and the same respiratory quotient as normal cells, were unable to multiply.

Desoxyribose nucleic acid, a viral component, was synthesized at a linear rate in infected cells determined by the rate of synthesis of viral peptides. Phosphate was assimilated exclusively in the desoxyribose nucleic acid synthesized. In normal cells, this synthesis accounted for 17 to 25 per cent of the phosphorus assimilated. The ratios of nitrogen, phosphorus and increments of desoxyribose nucleic acid in infected cells were the same as the ratios of these components in T_2r^+ virus, Therefore, infected cells synthesized the assimilated nitrogen and phosphorus into virus only. Since the components of virus were synthesized linearly, whether there were few or many virus particles within the cell, each virus particle formed within the cell did not become a center of new synthesis. Thus, virus synthesis occurred at a few enzyme sites of the host cell.

Virus multiplication in this system is clearly different from cellular multiplication. A virus may be defined as a parasite which organizes a specific enzymatic environment for its own synthesis.

Penicillin Sensitivity of Group A Beta Hemolytic Streptococci in Vitro and in Vivo. Dr. Horace M. Gezon, Chicago.

For a six month period all cultures of group A beta hemolytic streptococci obtained from patients in a children's hospital were tested in vitro for sensitivity to penicillin. The trough method in blood agar plates with standard penicillin G and commercial penicillin was used. A representative group of these strains of streptococci in either the mucoid or the matt phase of dissociation was tested for virulence and for the protective action of penicillin in white mice and 10 day old embryonated hen's eggs. In mice, the organisms were inoculated intracerebrally in 1,000 to 10,000 minimum lethal doses, followed immediately by penicillin in varying doses subcutaneously. In eggs the organisms were inoculated into the chorioallantoic fluid, immediately followed by varying concentrations of penicillin.

An attempt is made to correlate the results obtained by these three technics with the clinical course of the disease in patients.

Mineral, Fat and Nitrogen Metabolism in Infantile Diarrhea. Dr. Arthur W. Chung, New York.

The observations described were undertaken to throw light on the value of therapeutic oral starvation in cases of infantile diarrhea. Oral starvation, a generally accepted treatment, is usually carried out with two thoughts in mind: First, by resting the intestine the recovery of the digestive and assimilating function is hastened, and, second, it is useless to feed in the presence of hyperperistalsis, since the stimulation of digestive secretion caused by the food would result in additional electrolyte excreted into the intestine, while fat and nitrogen absorption would be interfered with, causing a loss of these substance to the body. Neither of these two arguments against oral feeding is supported by critical evidence.

The apparent amelioration of the diarrhea following oral starvation, which tends to impress the observer, does not prove that the disease is shortened thereby. Indeed, it is a common observation that the diarrhea returns when food is again administered. I should like to point out the lack of suitable statistical studies on the duration of diarrhea treated with and without oral starvation, a deficiency which should be remedied. I should also like to record the clinical impression that the duration of the digestive disturbance in these cases is determined by factors quite apart from the feeding.

If one grants the lack of proof for the assertion that oral feeding delays the return of intestinal function and admits the possibility that food per se does not damage such function, it becomes pertinent to proceed to the other question: Does the introduction of food in diarrheal states stimulate secretions and peristalsis to such an extent as to cause a net loss to the body or does it result in a net gain? This question I attempted to answer by chemical evidence.

Balance studies on 7 infants with parenteral diarrhea were carried out at different levels of oral feeding, measurements being made of total ash, water, sodium, potassium, calcium, chloride, fat and nitrogen. The results have been entirely consistent in showing that even in severe diarrhea, higher intakes resulted in increased absorption of every food constituent studied. Thus, the evidence supports a program of oral feeding rather than oral starvation in diarrhea. The extent to which oral feeding is practical may, of course, be limited by vomiting or distention. It is not suggested that the present practices of parenteral feeding should be curtailed, but since a completely satisfactory parenteral feeding has not yet been obtained it would seem desirable to utilize oral feeding to the greatest extent possible rather than to fear it.

Absorption of Emulsified Lipids from the Intestine in Steatorrhea. Dr. Charles D. May and Dr. Charles Upton Lowe, Boston.

The observation that vitamin A in propylene glycol administered orally elicited normal curves for vitamin A absorption in children with fibrosis of the pancreas stimulated investigation of the mechanism of this response. Frazer proposed that emulsified lipids may be absorbed intact through the intestinal mucosa, provided particles approach 0.5 micron in diameter. Mixtures of propylene glycol and vitamin A added to water produce particles of this appropriate size. Vitamin A in a finely emulsified state without propylene glycol with particle size from 2 to 5 microns was administered to children with fibrosis of the pancreas, and again normal curves for vitamin A absorption were obtained. This, along with the fact that propylene glycol alone elicited no elevation in plasma vitamin A, seemed to fit the hypothesis that the vitamin A was being absorbed through the intestinal mucosa independent of any lipolytic action. Variable responses were elicited in children with steatorrhea of other types.

Donovan J. McCune, M.D., *President*

Eighteenth Annual Meeting, Atlantic City, N. J., May 4-5, 1948

First Session

Tuesday Afternoon, May 4

President's Address: Refractory Rickets. DR. DONOVAN J. MCCUNE, New York.

In most of its aspects refractory rickets is identical with infantile privational rickets; the important difference is that unusually large doses of vitamin D are required to cure refractory rickets and to prevent recurrences. The disorder has to be distinguished from the several varieties of metabolic rickets caused by defective function of a single organ or viscus, such as the kidney, liver, pancreas and the intestine.

Inasmuch as treatment and prophylaxis demand concentrated preparations of vitamin D, refractory rickets did not emerge as a recognizable entity until vitamin D solutions of high potency became available about fifteen years ago. Numerous observations indicate that children are affected because of a hereditary peculiarity of unknown nature. The disease is apparently rare; the number of cases in the world's medical literature does not exceed 30; 10 patients with refractory rickets have been observed in Babies Hospital, New York city, during the last fifteen years. The pathologic anatomic changes are those characteristic of privational rickets.

The outstanding features are the appearance of signs of rickets toward the end of the first year or during the second year of life. Standard treatment for rickets does not effect cure. The disease persists into childhood and results in deformities of the skeleton of variable severity; of these, bowing of the legs and knock knee are the most frequent. Many patients are subjected to corrective osteotomy before the nature of the disorder is recognized; although the immediate result of such a procedure is satisfactory, the deformities soon recur because the fault in mineralization of the skeleton has not been controlled.

The amount of serum calcium is usually normal, the phosphorus level nearly always low; the serum phosphatase activity is invariably increased before treatment. Other results of chemical studies of the blood are normal. Roentgenographic examination reveals changes which vary from those characteristic of rickets, mild, moderate or severe, to those suggestive of chondrodystrophy.

Diagnosis depends on exclusion of disease of the kidney, liver, pancreas and intestine and of other disorders which adversely affect calcification of the bones. If these are excluded, favorable therapeutic response to large doses of vitamin D confirms the diagnosis. Some cases of chondrodystrophy may be confusing from the roentgenographic point of view; in such cases the therapeutic test is of critical importance.

Treatment requires from 50,000 to 500,000 U. S. P. units of vitamin D; there appears to be no significant difference between the result obtained with vitamin D_2 and that obtained with vitamin D_3. Large doses are not without hazard: The urine should be examined frequently with Sulkowitch's reagent and under the microscope. A positive reaction to the Sulkowitch test suggests caution; the appearance of calcium casts in the urinary sediment indicates that treatment should be stopped for the time, or at least the dose reduced. When possible, occasional determinations of serum calcium, phosphorus and nonprotein nitrogen content

should be secured until the child's ability to tolerate the dose being given is verified. Hypercalcemia is a sign of vitamin D excess and a warning of danger; increase in nonprotein nitrogen signifies vitamin D poisoning. If detected early, impairment of renal function can be reversed by discontinuance of treatment.

The outlook in cases of refractory rickets is uncertain. As far as is known all patients can be cured with large enough doses of vitamin D. Most patients require many times the usual prophylactic dose, for example, 25,000 to 50,000 U. S. P. units daily, to prevent relapse. In some children the disorder stops at puberty; in others cessation of longitudinal growth brings about a change from rickets—a growth disease—to osteomalacia, the pathologic equivalent of rickets in adults.

It is hardly possible to prevent the disease; it can be treated only after it is recognized. The need for large doses of vitamin D in cases of this kind should not be construed as an argument for the use of comparable amounts in everyday practice. Finally, when doses of this size are employed, it is the duty of the physician to watch the patient carefully in order to avoid vitamin D poisoning.

Measurement of Glomerular Filtration Rate in Premature Infants. Dr. Henry L. Barnett, Dr. Kendrick Hare (by invitation), Helen McNamara (by invitation) and Dr. Ruth Hare (by invitation), New York.

The high degree of regulation of water and electrolyte metabolism in young infants is effected by renal mechanisms which we are attempting to define. The two basic mechanisms for conservation of water and electrolytes, i. e., reduction of glomerular filtration rate and increased tubular reabsorption, can be differentiated only if glomerular filtration rate is measured. Simultaneous measurements of urea and inulin clearances in premature infants showed that urea clearances increased with increasing rates of urine flow throughout the entire range observed. Inulin clearances, on the other hand, showed only a slight increase with increasing rates of urine flow. From this observation, and from additional supportive data, we can conclude that inulin is probably excreted solely by the glomerulus in young infants, that the glomerular filtration rate is relatively independent of rate of urine flow and that urea clearances are not suitable for estimation of rate of glomerular filtration.

With the use of inulin clearances as a measure of glomerular filtration, it was shown that during periods of dehydration without loss of electrolyte, water is conserved, as in the adult, by increased tubular reabsorption of water (urine-plasma [U/P] ratios for inulin were over 200). The response of the infant's kidney to intravenous administration of "pitressin" indicates that this high degree of water reabsorption is effected by the antidiuretic hormone.

Although inulin clearances do measure glomerular filtration rate in young infants, they cannot be used for long term studies. Endogenous creatinine clearances calculated from plasma creatinine levels, as determined by two independent chemical methods, have shown the endogenous creatinine clearance to approximate the inulin clearance, although always slightly below it, in subjects ranging from newborn premature infants with clearances of approximately 4.0 cc. per minute to children approaching adolescence with clearances of approximately 80 cc. After this time, the creatinine clearance rises above the inulin clearance. It appears, then, that endogenous creatinine clearances may provide the essential technic whereby the basic renal mechanisms for control of water and electrolyte excretion may be studied over extended periods of time.

Acidosis in Young Infants: Effect of Ingestion of Ammonium Chloride. Dr. Harry H. Gordon, Denver, and Helen McNamara (by invitation) and Dr. Helen R. Benjamin (by invitation), New York.

The results of observations on the effect of ingestion of ammonium chloride on the acid-base excretion of 3 premature and 3 full term infants were presented. Two of the 3 premature infants showed a definitely diminished excretion of ammonia and increased excretion of sodium as compared with that of the full term infants. The results suggest that some premature infants may have a tubular deficiency.

One of the 2 infants with diminished ammonia formation and the third premature infant, the 2 smallest in the series, became listless, refused their feedings and showed depressed fontanels and diminished elasticity of the skin. These signs could not be correlated with changes in the carbon dioxide or chloride content of the serum nor with the presence or absence of an adequate urinary formation of ammonia and conservation of sodium. Since the infants who became clinically dehydrated gained weight while doing so, shifts of water and electrolytes from extracellular to vascular or intracellular compartments must have occurred. It is suggested that the tendency of young infants to acid intoxication may be conditioned by deficiencies in intracellular metabolism, as well as by renal dysfunction.

Osmolarity of Urine in the Infant. Dr. Elizabeth J. Dubs (by invitation), Buffalo.

Two groups of infants were studied in an attempt to evaluate the maximal osmolarity of the urine. Twenty infants with acute dehydration from diarrhea were compared with 16 convalescent infants whose fluid intake was restricted while the diet was maintained constant.

The osmolarity of the urine was determined by the method of freezing point depression as described by Gamble in his studies on the adult renal water requirement. Specific gravities obtained by the gradient tube were compared with the osmolarities and found to be roughly correlated, but with a wide scatter in the more concentrated specimens.

A composite graph of the group on restricted fluids showed a definite rise in osmolarity of urine with fluid restriction, but there were wide individual variations in concentrations obtained at particular levels of fluid intake. Moderate to severe dehydration developed in many of the infants, as indicated by an elevation in temperature not otherwise explainable, poor skin turgor or dry mucous membranes, loss of weight, or rise in the serum nonprotein nitrogen levels.

Of the 20 infants with diarrhea, osmolarity in only one fourth reached 1 osmol per liter or more, whereas 9 of the 16 infants on restricted fluid intake showed concentration of urine greater than 1 osmol per liter. The factors of age, degree of dehydration, loss in weight, fluid intake and serum nonprotein nitrogen, chloride and carbon dioxide levels, total anions and total protein showed no consistent relation to the osmolarity of urine.

The components of urine which contribute to osmolarity consist mainly of urea and electrolytes, most of which can be considered univalent. Analyses showed that the osmolarity can be calculated with fair accuracy by the addition of the urea and twice the amount of the fixed base. The result approximates the osmolarity obtained from the freezing point depression.

Two explanations for the low osmolarities demonstrated in the infants with diarrhea were offered. The renal impairment supposedly present in these infants

was shown to be temporary, since the nonprotein nitrogen levels returned to normal within three days. Chronic renal insufficiency, therefore, does not appear to be the probable explanation. The lack of body electrolytes needed to excrete a concentrated urine is suggested as a more likely cause of the submaximal osmolarities of the urine of infants with dehydration from diarrhea.

Studies on Nephrotic Edema: Water and Electrolyte Relationships During Diuresis. Dr. Niilo Hallman (by invitation) and Dr. Gretchen Hutchins (by invitation), Boston.

This report presents measurements of balance for water and electrolytes obtained from a 4 year old boy over a thirty day period of study following inoculation with measles. The patient exhibited the usual features of the nephrotic syndrome including massive edema at the outset of the period of study. On the fifteenth day after inoculation a large diuresis occurred and body weight fell from 22.1 to 14.9 Kg. in the course of five days. The electrolyte balances were determined directly from analyses of food, urine and stools. Change in body weight was taken as defining change in water balance.

The water and the sodium and chloride removed over the period of diuresis were observed to be closely parallel in terms of the usual concentrations of these electrolytes in extracellular fluid. Balances for the intracellular electrolytes, potassium and protein were not disturbed by the diuresis. Progressive retentions in the neighborhood of values which would be expected for growth were present throughout the thirty day period of study. These observations describe nephrotic edema as an extracellular event which does not appreciably alter the volume or the composition of intracellular fluid.

The concentration of sodium in the blood plasma rose extensively during the period of incubation, reaching a value of 157 millimols per liter. Then, during the period of active measles, sodium content decreased and reached its lowest value, 137 millimols per liter, just before the onset of diuresis. Over the remainder of the period of study the sodium level was moderately elevated, being approximately 145 millimols per liter. Additional data on plasma sodium obtained from other children with nephrosis are presented. Before diuresis the majority of the values found were below 140 millimols per liter, and during diuresis they were above this level. Thus, the data give no hint of a prediuresis rise in plasma sodium. They suggest rather that the sodium level rises as diuresis develops; in other words, that water removal is the initial event. The data, therefore, do not support the expectation that raising the plasma concentration of sodium would initiate diuresis.

Measurements of the colloidal osmotic value of the plasma were also obtained from the 4 year old patient, data on whose water and electrolyte fluctuations are presented. No change was observed before the onset of diuresis. During diuresis the colloidal osmotic value rose progressively from about 100 cc. of water to a final value of 276 cc. of water. As in the case of sodium, this rise was apparently a consequence, rather than the cause, of water removal.

These observations do not render less inscrutable the initiating mechanism of diuresis in nephrosis.

Lysozyme in the Urine of Nephrotic Children. Dr. Armine T. Wilson and Dr. William P. Hadley (by invitation), Wilmington, Del.

Lysozyme is present in most of the tissues and fluids of the body, but it had not been found in urine, sweat and cerebrospinal fluid of normal persons. Fleming

reported the presence of lysozyme in a single specimen of "urine containing much albumin and pus." No other studies of urinary lysozyme appear to have been made.

A search for lysozyme in samples of urine from children with the nephrotic syndrome revealed the protein to be present in considerable quantity in many. The urinary lytic agent has been identified with the lysozyme of egg white on the basis of the bacteria which both are capable of lysing, of the chemical properties of the two and of their inhibition by sodium dodecyl sulfate.

A method for the quantitative determination of lysozyme in urine has been devised in which satisfactory control of p_H, temperature, electrolyte concentration and density of the suspension of the test organism, Micrococcus lysodeikticus, has been achieved. Lysozyme concentration is expressed in units per cubic centimeter of urine, a unit representing the reciprocal of the greatest dilution of urine which produces visible lysis.

Single specimens of urine were obtained from 235 Philadelphia school children. No lysozyme was detected in 198 of these specimens. In the remaining 37 it was present in varying concentration, but in no instance did it exceed 32 units per cubic centimeter.

Single specimens from 103 children with a variety of acute and chronic diseases were obtained from the Temple University Hospital and St. Christopher's Hospital for Children, Philadelphia, through the courtesy of Dr. Waldo E. Nelson, and from the Harriet Lane Home, Baltimore, through the courtesy of Dr. Lewis Thomas and Dr. Francis Schwentker. Of these 103 specimens, 80 contained no lysozyme. Twenty-one contained lysozyme in amounts not exceeding 32 units per cubic centimeter. In addition, 1 sample, from a 2 month old premature infant with pneumonia, contained 64 units per cubic centimeter, and 1, from a patient with typhoid fever who had 5.6 Gm. of protein per liter of urine, contained 256 units of lysozyme per cubic centimeter.

Serial studies over a period of four months on 13 children with the nephrotic syndrome revealed that 6 of them failed to reach levels higher than the maximum encountered among the Philadelphia school children, but that 7 of them reached levels of from 64 to 1,024 units. In general, the patients with high urea clearances excreted small amounts of lysozyme, while those whose urea clearances were reduced excreted large amounts of lysozyme. There was no correlation between quantitative lysozyme excretion and albuminuria, hematuria, plasma albumin and total protein levels, plasma amino acid values, clinical edema or natural or albumin-induced diuresis; nor did significant changes in excretion of lysozyme precede or follow the acute infectious episodes which occurred in many of these children.

Renal Function in Renal Rickets. Dr. Erika Bruck, Alverna Baumler (by invitation) and Dr. Thomas S. Bumbalo (by invitation), Buffalo.

Results of studies of renal function are reported for a 32 month old girl with pneumonia, severe acidosis with coma, tetany and severe rickets in spite of a history of average intake of vitamin D. Polydipsia and tremors of the hands were prominent and persistent. Her blood pressure was normal, her development retarded. There was albuminuria, and the specific gravity of the urine was always low.

The child was always in acidosis, except at one time when she was receiving 100 milliequivalents of alkali daily, which resulted in alkalosis. Her serum chloride was always slightly elevated; the serum calcium level remained low throughout

her stay in the hospital but was normal a year later. Serum phosphorus content was normal and the nonprotein nitrogen level considerably elevated. The rickets healed under treatment with alkali and high doses of vitamin D.

The glomerular filtration rate, the tubular capacity to excrete para-aminohippurate and the tubular capacity to reabsorb glucose were determined by clearance tests. The glomerular filtration rate was 11 per cent of normal. The urea clearance approximated the mannitol clearance, less than 2 per cent of the filtered urea being reabsorbed. Low reabsorption of water with resulting large urine flows might explain the failure to reabsorb urea. The tubular capacity to excrete para-aminohippurate was not significantly different from 0.

Filtration and reabsorption of water, sodium and chloride were studied with and without saline infusions. The reabsorption of water from the small amount of glomerular filtrate was only 74 per cent of the filtered amount on the average, less than patients with severe diabetes insipidus (but normal glomerular filtration) reabsorb. On several occasions, the water reabsorption went down to about 50 per cent of the filtered amount, i. e., below the so-called obligatory water reabsorption, which is assumed to take place in the proximal tubules and is usually estimated at 66 to 80 per cent of the filtered water. The reabsorption of sodium, chloride and calcium was better than that of water; although a low of 80 per cent of the filtered sodium and chloride was reabsorbed during infusions, restriction of sodium chloride resulted in good reabsorption. The specific gravity and the osmolarity of the urine were always below those of the plasma water, while the fluid reabsorbed by the tubules had a higher concentration of total solids and of all individual constituents except urea and phosphorus than the plasma water. During a concentration test the highest specific gravity of the urine was 1.008.

The reabsorption of phosphorus was low; it was three to eight times as high in 1948 as it had been in 1947, but the values, both absolute and in percentage, for the filtered amount were still below any observed for experimental animals (in the literature). However, the multiple factors influencing phosphorus reabsorption were not controlled sufficiently to decide whether there was a specific defect in the reabsorption mechanism for phosphorus, nor could the improvement in reabsorption one year after the initial observations be correlated with the healing of the rickets.

The response of the base-defending mechanisms of the kidney to calcium chloride given orally was tested. One gram of calcium chloride daily resulted in severe acidosis on the fourth day. On the third day the p_H of the urine was 6.45; the titratable acidity was 2.8 milliequivalents per twenty-four hours, and the excretion of ammonia was negligible.

It is assumed that a reduction in the number of nephrons may account for the reduction in the filtration rate and the absolutely low, but relatively good, reabsorption of sodium, chloride, calcium and glucose. In addition, there seems to be specific deficiency of the capacity to reabsorb water, although the kidneys are capable of creating an osmotic difference between the reabsorbed and the excreted fluid. The virtual absence of any ability to excrete para-aminohippurate and to produce ammonia, also the severe deficiency of the acidification mechanism, are seen as additional qualitative defects, probably of the distal tubules.

The functional deficiency was not progressive; a congenital defect rather than a nephritic process was assumed to be the cause of the physiologic disturbances.

Experimental Observations on Grafting of Blood Vessels. Dr. Robert E. Gross, Dr. Elliott S. Hurwitt (by invitation), Dr. Alexander H. Bill (by invitation) and Dr. Edmund Converse Peirce Jr. (by invitation), Boston.

Observations were made on the grafting of arteries from one dog to another. A segment of the abdominal aorta from a donor dog was used to replace a section of the abdominal aorta of a recipient animal. A total of 63 such grafts was made and studied. The work was divided into three separate sets of observations; in the first, vessels were removed from a donor animal and freshly implanted in the second dog; in the second, the segments of vessels were preserved by freezing before being implanted; in the third, the arterial segments were preserved by maintaining them in a special solution just above freezing before placing them in a second animal.

In the first set of experiments there were 27 grafts. The aortic segments, after being removed, were kept (moist and in a common refrigerator) for periods varying from two to seventy-eight hours and then implanted in recipient dogs. The recipient animals were kept for periods up to as long as one year. When the material for the grafts had been kept for only a few hours, there was an excellent chance of survival of the grafts in the recipient animals. When material had been kept for approximately six hours and then implanted, only about two thirds of the grafts survived and remained in satisfactory condition. When the specimens of aorta were kept from eighteen to seventy-eight hours before being implanted into recipient animals, the vast majority of the dogs died from thrombosis of the graft or dehiscence at the suture lines.

In the second portion of the work, the blood vessels from donor dogs were quickly frozen to —72 C. (—97.6 F.) and were then stored at this temperature for periods varying from two to thirty-five days before being implanted into recipient dogs. Twelve such grafts were made. Three quarters of these dogs died in five to thirty days after operation from hemorrhage at the suture line. Two grafts were partially thrombosed. One graft kept for six months and showed moderate intimal sclerosis. It was felt that storage of vessels by freezing would not be a satisfactory method for preserving arterial grafts.

In the third part of the work, aortic segments were taken from donor dogs and stored in flasks, the graft being just covered with an electrolyte solution, to which had been added glucose (1 per cent) and dog serum (10 per cent), a buffer, as well as penicillin and streptomycin (giving a concentration of 50 units of each per cubic centimeter), and, finally, a phenol red indicator so that changes in the p_H of the solution could be visibly determined. Each flask with its solution containing a segment of vessel was stored in a constant temperature ice box at 1 to 4 C. (33 to 39 F.). Tissue culture studies on segments of vessels preserved in this way showed that vessels were viable and that fibroblastic proliferation could be demonstrated for as long as forty days in most instances, while in some cases it could be shown for a longer time. Segments of vessel which had been stored in this manner for periods of from two to ninety-eight days were implanted into recipient dogs. Twenty-four such grafts were made, and the recipient animals were kept from four days to eight months. There were no deaths from dehiscence or thrombosis of the grafts. Three animals had minor thrombi at the lines of anastomosis. All the remaining grafts were known to be carrying blood for periods as long as eight months. These vessels were examined in the living dogs by aortagrams and were carefully studied at autopsy at the time of death or killing of the animals. The experiments indicated that arteries can be stored satisfactorily by this method in the cold for slightly more than a month and can still be used for purposes of grafting.

With the belief that the latter method of arterial preservation would be applicable to human subjects, segments of arteries (obtained within a few hours from human subjects who died in automobile accidents) were placed in 6 children. These grafts bridged gaps between the arterial system and the pulmonary artery when it was desired to establish an aorta-pulmonary artery shunt for alleviation of the cyanotic state of tetralogy of Fallot. One of these patients died twelve days after operation, largely from the effects of "dicumarol" therapy. A second died two days after operation from cardiac decompensation. The grafts in both instances were patent. In the remaining 4 patients the grafts are apparently carrying blood and have been in place from two weeks to three months. Evidence that these grafts are patent can be adduced from the fact that all the children have continuous murmurs (which previously did not exist), and that the cyanotic states have been definitely improved.

Resection of Rectum and Rectosigmoid with Preservation of the Sphincter. Dr. Orvar Swenson (by invitation) and Dr. Edward Neuhouser, Boston.

Thirty-one patients with clinical diagnosis of Hirschsprung's disease, or congenital megacolon, were studied at the Children's Hospital in the past five years. By a special type of barium sulfate enema, parts of the sigmoid and rectum were demonstrated to be abnormal in each of these patients. The abnormality consisted of narrowness of the lumen and disorganization of the peristaltic movements. The clinical course and the roentgenographic examination made us feel that these patients had a functional obstruction of the colon.

Severe obstipation in 3 patients made colostomy necessary, and in each instance the patient improved and behaved as any patient relieved of obstruction of colostomy. Closure of the colostomy opening was performed in these 3 patients, with rapid recurrence of their disease. Reopening gave complete relief of symptoms. In an additional 8 patients, colostomies were done with complete recovery.

Our experience demonstrated the futility of closing the colostomy opening in these patients. It became evident that the abnormal portion of the bowel must be removed to permit normal function and continuity of the intestinal tract. On the basis of the roentgenographic studies, the abnormal section extended down to the anus in most of these patients. Removal of this abnormal segment of bowel with preservation of the anal sphincter cannot be accomplished with the conventional types of resection. A new method of resection was devised which permitted the removal of the abnormal part of the bowel down to the anus with full preservation of the sphincter.

This procedure was tested in the laboratory on a series of dogs and found to be satisfactory. It has now been used on 12 patients with congenital megacolon. There have been no postoperative deaths. All patients have normal sphincter control. All are now having spontaneous bowel movements without the aid of diets, liquid petrolatum or laxatives. The longest period of postoperative observation was one year.

Gargoylism: Study of Pathologic Lesions and Clinical Review of Twelve Cases. Dr. Stuart Lindsay (by invitation), San Francisco, Dr. William A. Reilly, Little Rock, Ark., and Thelma J. Gotham (by invitation) and Dr. Richard Skahen (by invitation), San Francisco.

This paper will be published in full in a later issue of the American Journal of Diseases of Children.

Second Session

Wednesday Morning, May 5

Relation of Chickenpox and Herpes Zoster: Studies with the Electron Microscope. Dr. Geoffrey Rake (by invitation), Dr. Harvey Blank (by invitation), Dr. Lewis L. Coriell (by invitation), Dr. Frederick P. O. Nagler (by invitation) and Dr. T. F. McNair Scott, Philadelphia.

Elementary bodies are present in the vesicle fluid of lesions of the various clinical forms of herpes zoster. These elementary bodies resemble closely those seen in chickenpox, both in shape and in size. In the few vesicle fluids so far examined, these elementary bodies tended to be scanty when twenty-four hours, or longer, elapsed since the first appearance of the lesions from which the fluid was removed. In 1 case in which the fluid was obtained as early as twelve hours, elementary bodies were numerous and were observed to disappear later. Heavy agglutination of these elementary bodies can be produced with convalescent serum from cases of either chickenpox or herpes zoster. In addition to the agglutination, each separate particle tends to be covered with a coating of serum. Some clumping of the virus bodies is apparent even in vesicle fluid itself and on the addition of acute phase or adult serum. One vesicle fluid was examined from a case of herpes zoster which apparently initiated an outbreak of chickenpox. Material from 3 of the cases of chickenpox was also examined and showed scanty but characteristic brick-shaped bodies which were identical with those seen in the original case of herpes zoster.

Nature of the Action of Streptomycin on Sensitive Hemophilus Influenzae. Dr. Hattie E. Alexander and Grace Leidy (by invitation), New York.

The speed of the injurious effect of streptomycin on Hemophilus influenzae, type B, and the factors influencing it have become important since the recognition that vestibular damage can follow only four to five days of streptomycin therapy.

This report presents data on the speed and character of the action of streptomycin on sensitive H. influenzae cells and the influence of the size of the population and concentration of streptomycin on the time required for this injurious effect.

The results demonstrate that members of H. influenzae populations are not uniformly sensitive to streptomycin. More than 99 per cent are susceptible to 1.6 microgram per cubic centimeter; the larger the population, the wider is the variation in resistance of the small fraction surviving.

Streptomycin in concentrations between 10 and 100 micrograms per cubic centimeter exerts a rapid lethal action, and the greater the concentration of the antibiotic substance the greater the speed. Significant increases in population size prolong the time required for bactericidal action.

The sizes of the bacterial populations observed in the spinal fluid of patients with influenzal meningitis were demonstrated to be comparable with those studied in these in vitro experiments. It was shown that after introduction of 25 mg. of streptomycin intrathecally a concentration of approximately 100 micrograms per cubic centimeter is maintained for at least three hours. The aforementioned data, together with these observations, suggest that a twenty-four hour period of streptomycin therapy will be adequate for elimination of all sensitive organisms. The addition of sulfadiazine can be expected to eliminate any minute fraction persisting after this period, as well as any highly resistant mutants which may be present in large populations.

Effect on Herpes Virus of a Filtrate Obtained from Salmonella Typhosa.

Dr. Horace L. Hodes and Helen Zepp (by invitation), Baltimore.

It is well known that herpes labialis is frequently associated with certain infectious diseases. This association is particularly striking in the case of pneumococcic pneumonia and meningococcic meningitis. In contrast, infection with herpes virus rarely occurs in patients with typhoid fever. A consideration of this fact suggested the possibility that Salmonella typhosa might produce a substance or substances which could neutralize or inhibit herpes virus.

Experiments were undertaken to explore this possibility. A strain of S. typhosa freshly isolated from the blood of a patient with typhoid fever was cultured at 37 C. (98.6 F.) in broth composed of a hydrolysate of casein and soybean proteins, salts, dextrose and water. At the end of fourteen days' incubation, the organisms were removed by centrifugation and filtration through a Seitz filter. The sterile filtrate was mixed with herpes virus obtained from the brain of a mouse which died after intracerebral injection of HF strain of the virus. The mixture containing virus in dilution of 1 : 10 was then incubated at 37 C. for two hours and inoculated onto the left cornea of 14 rabbits. At the same time a 1 : 10 dilution of the virus in untreated broth after the same incubation period was inoculated into the right eye of each rabbit. In each of the 14 rabbits typical herpetic lesions developed in the eye which had been inoculated with virus in untreated broth, while such lesions occurred in only three of the eyes inoculated with virus in typhoid-broth filtrate.

In a number of experiments the neutralizing effect of typhoid filtrate prepared in the manner described was demonstrated by intracerebral injection into mice. Mixtures containing virus in final dilutions of 1 : 200, 1 : 2,000 and 1 : 20,000 in untreated broth were prepared and incubated at 37 C. for two hours. Mixtures containing these same virus dilutions in typhoid filtrate were incubated in the same manner. Ten mice were given intracerebral injections with each virus-broth and virus-filtrate mixture, using 0.03 cc. for each mouse. In a typical experiment a dilution of the virus in untreated broth of 1 : 11,000 was found to be lethal for 50 per cent of the mice given injections, while a 1 : 200 dilution of the virus in typhoid-broth filtrate was required to produce this fatality rate. In this instance the lethal effect of the virus in untreated broth was roughly 50 times as great as that of the virus in typhoid-broth filtrate. In other experiments the neutralizing effect of the typhoid-broth filtrate on the virus caused approximately a hundredfold reduction in the virulence of the virus.

Experiments recently completed indicate that the neutralizing action of the typhoid-broth filtrate described does not depend on prolonged incubation at 37 C. Incubation of the virus with filtrate at room temperature for thirty minutes causes demonstrable neutralization of the virus.

The neutralizing action of S. typhosa is not shared by all members of the genus Salmonella. Filtrates prepared from one strain of Salmonella kunzendorf and Salmonella bredeney had no demonstrable effect on herpes virus, and one strain of type VII pneumococcus also showed no neutralizing action.

The aforementioned experiments show only that typhoid-broth filtrate exerts a definite neutralizing action when placed in contact with herpes virus before inoculation is made into the test animal. No effect on the virus is obtained when virus and filtrate are inoculated at different sites. This is true whether the filtrate is inoculated before or after the virus is injected. The reason for this difference is not known, but two main possibilities are suggested. The first is that in these circumstances the neutralizing substances are inactivated in the body fluids and are

therefore unable to affect the virus. The second possibility is that they are so diluted in these fluids as to fall below their minimal effective concentration. In any case, the identification and isolation of the substances responsible for the in vitro neutralization would be of interest. Such experiments are now being undertaken.

Cross Infections in Infants' Wards and Their Control by the Use of Triethylene Glycol Vapor. DR. C. G. LOOSLI (by invitation) and DR. MARGARET H. D. SMITH (by invitation), Baltimore.

The wartime investigations of the Commission on Air-Borne Infections of the United States Army Epidemiological Board (under the direction of Dr. O. H. Robertson) included a study of the use of triethylene glycol vapor alone for the prevention of cross infections in hospital wards. Because of the high incidence of such infections and the ease of keeping young patients confined to bed, the present study was carried out, at the invitation of Dr. E. A. Park, on the infants' wards of the Johns Hopkins Hospital, Baltimore, from November 1945 to May 1946. Two identical wards of sixteen to eighteen cribs provided a test and a control unit, identical with respect to size, ventilation, humidity, routine ward isolation and number and types of patients admitted; however, the atmosphere in the test ward was maintained at a 55 to 70 per cent saturation with triethylene glycol vapor.

Bacteriologic analyses were made twice a week of the environment and of the nasopharyngeal flora of patients, hospital staff and personnel and visitors. Particular attention was paid to the presence and spread of beta hemolytic streptococci (which were grouped and typed according to the Lancefield technic), pneumococci (which were likewise typed) and to the occurrence of a previously undescribed encapsulated gram-negative bacillus of the Friedländer-aerogenes group. All infections which developed in patients while in the hospital were classified as clinical infections (when accompanied with such objective signs as common cold, otitis, diarrhea or fever) or as inapparent bacterial infections. Soon after the start of the study it became evident that the frequent use of sulfonamide compounds constituted a factor which must be taken into consideration in the evaluation of our results. The conclusions which we were able to draw from this study were as follows:

1. No ill effects whatever could be attributed to the prolonged exposure to triethylene glycol vapor.

2. The total difference in number of new infections arising in the two wards was approximately 2 to 1 in favor of the test ward. This differential, though favorable, was not statistically significant.

3. Analysis of the patients on the basis of whether or not they were receiving chemotherapy showed only a 35 per cent difference in the group not receiving drugs, and a 78 per cent difference in favor of the glycol ward in the group receiving chemotherapy.

4. In each instance of bacterial cross infection, clinical or inapparent, another patient in the ward carried a pneumococcus or streptococcus of the same type. The source was usually discovered to be, in the case of the pneumococcus, a patient with chronic sinusitis or bronchitis accompanied with profuse nasal discharge; in the case of the beta hemolytic streptococcus the source was often a patient with an exudative cutaneous infection or purulent otitis media.

5. There was no evidence that any cross infection was acquired from hospital personnel or visitors.

Primary Atypical Pneumonia in Infants and Children. Dr. Richard G. Hodges and Dr. Oliver K. Scott (by invitation), Cleveland.

The study was based on 74 children admitted to the Babies and Childrens Hospital, Cleveland, during the winter of 1947-1948. An arbitrary division was made into the following three groups: (1) 33 patients who showed a clearcut response to penicillin therapy; (2) 21 patients who showed no response to penicillin and 9 patients who had an equivocal response; (3) 11 children in whom the diagnosis of pneumonia was made on admission was not substantiated. Acute and convalescent phase serums were obtained from all children and were tested for the presence of cold hemagglutinins and agglutinins against Streptococcus MG. In only one instance did the test with Streptococcus MG give information not furnished by the cold hemagglutinins.

In the first group, which was designated as bacterial pneumonia, only 1 child had a cold hemagglutinin titer greater than 1:32. This 7 year old girl had a history suggestive of nonbacterial pneumonia followed by pneumococcic pneumonia. In the second group, which was considered as nonbacterial pneumonia, one half of all patients, and three fourths of patients 3 years or more of age, showed titers of 1:64 or higher. In the third group, in which the diagnosis was other than pneumonia, 2 patients had titers positive for cold hemagglutinin and both carried the diagnosis of erythema multiforme exudativum. On the basis of the cold hemagglutinin studies, it was concluded that primary atypical pneumonia is a common disease of infancy and childhood, that positive titers are less frequent below the age of 3 years and that the clinical picture is similar to that seen in adults.

A Diagnostic Test for Pancreatic Insufficiency. Dr. Harry Shwachman and Dr. Halvor N. Christensen (by invitation), Boston.

The present study is an attempt to establish a simple diagnostic procedure for pancreatic insufficiency. Enough variation has been noted in the glycine content of plasma after a gelatin meal in patients with and without pancreatic insufficiency studied to date to permit the differentiation. The glycine was determined by the method of Alexander, Landwehr and Seligman. For comparison, alpha-amino-nitrogen was determined by the manometric ninhydrin method. West, Wilson and Eyles suggested the aminonitrogen response following a test feeding of casein or gelatin as a possibly useful diagnostic procedure. In view of the high glycine content of gelatin, proportionately much higher rises occurred in the plasma glycine than in the alpho-aminonitrogen. The glycine determination also had the advantage of being a simpler procedure requiring less specialized skill and apparatus, and less plasma.

A group of patients (15) not having pancreatic fibrosis showed in samples of blood taken one and two and one-half hours after the feeding of 1.5 Gm. of gelatin per kilogram, a quadrupling of the fasting concentration of glycine in plasma. In a group of patients with pancreatic fibrosis (14) less than a doubling of the fasting concentration of glycine was noted. One exception was encountered in a patient with pancreatic fibrosis associated with hepatic disease in that the rise in glycine nitrogen at the end of two and one-half hours was equal to the rise observed in the control group. When pancreatin was fed with the gelatin in the patients with pancreatic fibrosis, the glycine was increased by more than four times (as an average) the fasting concentration. This response supports the value of pancreatin in improving the nutrition of patients with pancreatic fibrosis.

Effect of Pancreatin on Curves for Vitamin A Absorption As an Aid to Diagnosis in Pancreatic Deficiency. Dr. Gordon E. Gibbs (by invitation), San Francisco.

The concentration of vitamin A in the plasma was determined in the fasting state and three and five hours following test doses of 7,000 units of vitamin A per kilogram as halibut liver oil U. S. P. Such tests were done with and without administration of "enteric-coated" pancreatic granules in a dose of 0.15 Gm. per kilogram. Among the 18 infants and children in whom pancreatic deficiency was manifested by concentrations of trypsin of less than 0.7 per cent of the average normal value in the duodenal fluids, the curve for vitamin A was higher with pancreatin than without. The average rise with pancreatin was 3.6 times the fasting level. Without pancreatin the average rise was only 0.08 times the fasting level. In 13 children with the celiac syndrome and normal pancreatic concentrations of trypsin, the corresponding average rises were 0.25 when pancreatin was given and 0.68 when pancreatin was not given. In 15 control infants and children, the average rise was 4.8 when pancreatin was given and 4.1 when it was not given. Thus, pancreatin had little, if any, effect on vitamin A curves in normal patients or on the low curves of a patient with nonpancreatogenous celiac syndrome.

This effect of pancreatin may have some diagnostic usefulness in distinguishing pancreatic from nonpancreatic steatorrheas. There is, however, an equivocal range. Two of the 13 cases of nonpancreatic celiac syndrome had a pair of curves showing a small apparent advantage from pancreatin comparable to that observed in 4 of the 18 cases of pancreatic deficiency. Repetition of the curves would largely insure against a false diagnosis from an occasional erratic curve.

The curve for vitamin A with pancreatin would seem a useful method of detecting celiac disease complicating a fibrocystic disease. The effect of pancreatin on the curve for vitamin A in pancreatic deficiency tends to encourage the use of pancreatin in treatment of this condition.

In the duodenal drainages used to determine pancreatic deficiency, simultaneous, separate gastric and duodenal aspiration has been done, minimizing contamination of the sample of duodenal fluid by the gastric fluids. Earlier, two separate 12 F rubber tubes were used. Later, a bilumen tube of 12 F over-all size, containing two equal lumens side by side, was found to be even more practical.

Trypsin was determined by use of a hemoglobin substrate (made from overage bank blood) and colorimetric determination of the liberated tyrosin (Anson, M. L.: *J. Gen. Physiol.* **22**:79, 1939). Lipase was determined using benzyl butyrate, which has the advantage of speedy reaction and reproducibility of the dispersion (Balls, A. K.; Matlack, M. B., and Tucker, I. W.: *J. Biol. Chem.* **122**:125, 1937). Amylase was determined by Willstätter's volumetric hypoiodite method (Schmidt, C. R.; Greengard, H., and Ivy, A. C.: *Am. J. Digest. Dis. & Nutrition* **1**:618, 1934). Lipase concentrations correlated well with trypsin in pancreatic deficiency. Amylase concentrations in celiac disease did not deviate significantly from normal.

Intestinal Absorption of Vitamin A from Oily and Aqueous Mediums in Patients with Celiac Syndrome. Dr. Wayne H. Danielson (by invitation), Dr. Edward L. Binkley (by invitation) and Dr. Harold D. Palmer, Denver.

Vitamin A is absorbed poorly from the intestinal tract in patients with the celiac syndrome when given in an oily medium. In most instances the curves for vitamin

A absorption were just as flat in patients with idiopathic celiac disease as they were in patients with cystic fibrosis of the pancreas.

Dispersion of the oily medium containing the vitamin A on "dextri-maltose" improves the absorption of the vitamin only slightly in patients with cystic fibrosis of the pancreas. In every instance the absorption curves rose slightly above the control curves for percomorph liver oil N. N. R. ("oleum percomorphum"), but they all remained well below the lower limit of a normal response 50 "620 units." However, when these same patients were given vitamin A acetate or vitamin A alcohol dispersed on "dextri-maltose" the absorption curves rose to a level well above the lower limit of a normal response. There was no consistent difference in the responses to the vitamin A acetate and to vitamin A alcohol.

Patients with idiopathic celiac disease are unable to absorb vitamin A readily from either an oily or an aqueous medium. When vitamin A alcohol in 70 per cent propylene glycol, vitamin A in a water-paste emulsion, vitamin A alcohol or vitamin A acetate dispersed on "dextri-maltose" was given to these patients the absorption curves rose only slightly above the control curves for percomorph liver oil. In all instances the curves remained low and failed to reach the lower limit of a normal response. There was no consistent difference between the response to the vitamin A alcohol and that to the acetate.

The failure of patients with idiopathic celiac disease to absorb vitamin A readily when it was given in either an oily or an aqueous medium supports the suggestion made by May, McCreary and Blackfan that the defect in absorption in these patients is within the intestinal mucosa.

Sulfur Amino Acid Requirement of the Infant. Dr. Anthony A. Albanese (by invitation), Dr. L. E. Holt Jr., Virginia I. Davis (by invitation), Dr. Selma E. Snyderman (by invitation), Marilyn Lein (by invitation) and Emilie M. Smetak (by invitation), New York.

The cystine and methionine requirements of the infant were determined by measuring the nitrogen retention and gains in weight on a diet deficient in these two amino acids as the principal source of nitrogen. This diet was supplemented with varying proportions of *l*-cystine and *l*-methionine.

Five male infants (4 to 11 months of age) were studied. In 3 infants who received no cystine supplements the nitrogen retention and gains in body weight were restored to normal levels by an intake of 85 mg. of *l*-methionine per kilogram of body weight. In 2 infants who received a 1 per cent *l*-cystine supplement the nitrogen retention and positive change in weight were restored to normal values by an intake of 65 mg. of *l*-methionine per kilogram of body weight.

These observations suggest that cystine is capable of stimulating growth only when methionine is present in suboptimal amounts and that about 20 per cent of the methionine needs can be met by cystine. Moreover, it appears from these results that the quantities of sulfur amino acids provided by the commonly employed infant formulas prepared from cow's milk are adequate. On the basis of calculations from the available data on the sulfur amino acid content of human milk, it would appear that the breast milk provides only a meager margin of safety during the early months of life and does not provide an adequate quantity of the sulfur amino acids in the latter part of the first year. The margin of safety is considerably greater in the artificially fed infant.

Metabolism and Disposal of Casein Hydrolysate Administered Intravenously. Dr. William M. Mulholland (by invitation) and Helen Fox (by invitation), Buffalo.

In view of the increasing use of protein hydrolysates as complete sources of protein requirements, there is a need for a better understanding of the metabolism of these products and the manner in which they are disposed of by the body. In the investigations to be reported, qualitative and quantitative data were obtained regarding (1) water balance, (2) nitrogen balance and (3) respiratory metabolism. The experiments were carried out on rabbits which were given eight hour infusions of a casein hydrolysate ("amigen").

The animals were prepared for experiment in the following way: All were maintained on a standard pellet diet known to be adequate in all food, vitamin and mineral constituents. Two to four days prior to experiment, a specially constructed glass cannula was surgically inserted into the bladder to enable continuous collections of urine. Animals were fasted, but permitted water as desired for twelve to fourteen hours before experimentation.

The experiment consisted of an eight hour intravenous infusion of 1.0 Gm. "amigen" (10 per cent solution) per kilogram per hour. Control studies consisted in the intravenous infusion of a 2.57 per cent urea solution in isotonic sodium chloride solution. Both solutions contained equivalent amounts of nitrogen and water, and both were given at the rate of 10 cc. per kilogram per hour.

Results were as follows: Animals given "amigen" proved to be in distinct positive water balance, whereas those given the urea solution were able to balance output against intake quite closely. Explanation for this difference lies in the fact that the animal given infusions of "amigen" had less urea presented for excretion during the experimental period. This is shown by the fact that the blood urea nitrogen did not rise as high and less urea was found in the urine. Since less urea required excretion, the water necessary for its excretion was decreased and a positive balance resulted.

Calculations of nitrogen balance showed a deposition in the tissues of 555 mg. total nitrogen in the animals given infusions of "amigen." Those given urea showed a negative balance of 441 mg. The latter figure is taken to represent the nitrogen contributed by endogenous protein catabolism, for it corresponds closely with the excretion of control animals given infusions of isotonic sodium chloride solution. The positive balance therefore represents both anabolism and storage, as well as a reduction in catabolism.

The respiratory quotient for rabbits given "amigen" averaged approximately 0.72. This figure is extremely low. It is lower than the usually accepted respiratory quotient of protein metabolism (0.80), and it is even lower than a theoretically calculated respiratory quotient for the complete deamination and oxidation of the sum of the individual amino acids present in "amigen" (0.85). Explanation for this seemingly anomalous result is lacking.

A dynamic method for the study of the metabolism of amino acids is presented. Positive water and nitrogen balances were demonstrated for animals receiving a protein hydrolysate in contrast to those given infusions of a similar water and nitrogen load in the form of a 2.57 per cent urea solution. Explanation of the difference appears to lie in the smaller amount of urea presented for excretion in the animals given infusions of the hydrolysate. The suggestion is offered that a more efficient nitrogen balance might be obtained by giving less hydrolysate, but continuing the infusion over longer periods with provision of full caloric needs in other forms.

Third Session

Wednesday Afternoon, May 5

Megaloblastic Anemia in Infancy. Dr. Charles D. May, Boston, and Dr. E. N. Nelson (by invitation), Dr. R. A. Aldrich (by invitation), R. J. Salmon (by invitation) and Dr. R. I. Lienke (by invitation), Minneapolis.

Zuelzer (1946) in an excellent study of megaloblastic anemia in infancy pointed out the importance of examination of the marrow in establishing the diagnosis and emphasized infection as among the possible etiologic factors. Aldrich and Nelson (1947) reported on a group of infants with megaloblastic anemia whose diets were uniform in composition. The synthetic milk which they were fed was designed to be similar to human milk. It was intended that ascorbic acid be given with this product but it was not included for these infants. Amato (1946) described this same syndrome as it developed in 25 infants fed exclusively at the breasts of mothers whose health was said to be normal. Fourteen of the 25 infants originally reported on by Zuelzer had been reared on breast milk or artificial foods of similar composition. However, a variety of diets have been implicated, including goat's milk.

We are endeavoring to determine whether some hematopoietic substance is at times suboptimal in diets of infants, or whether there is a faulty utilization of such a substance in some infants. Particular attention is being given to the role of ascorbic acid, pteroylglutamic acid, "extrinsic" and "intrinsic" factors, gastrointestinal function and protein metabolism.

Pigs, in which megaloblastic anemia can develop, did not show the condition when fed adequate protein and calories in the form of a synthetic infant food with composition similar to human milk, or even when fed a low protein and caloric diet for ninety days using the same food, although growth was decidedly stunted. These animals synthesize ascorbic acid and the level in the blood remained normal.

Two infants with megaloblastic anemia presenting the same background as that described by Aldrich and Nelson were studied in detail. They were deficient in ascorbic acid. In 1 infant the marrow became megaloblastic while under observation, even though the deficiency of ascorbic acid had been corrected. The marrows remained megaloblastic in spite of daily administration of 200 mg. of ascorbic acid intramuscularly in 1 infant. The excretion of pteroylglutamic acid in the urine of these 2 infants was of the same magnitude as we noted in normal infants of the same age, approximately 0.4 microgram per day. The effect of relatively purified erythrocyte maturation factor was tested. Two U. S. P. units to 1 infant and 4 U. S. P. units to the other were administered daily intramuscularly in the form of "reticulogen" (a parenteral liver extract with vitamin B_{12} found to contain 0.75 microgram pteroylglutamic acid per U. S. P. unit). The diets were kept as they had been during the development of the anemia except for the addition of ascorbic acid. Megaloblastic changes in the marrow completely disappeared in six days and the symptoms of the patients were promptly relieved.

Zuelzer demonstrated that pteroylglutamic acid can cure this type of anemia just as it can restore the marrow to normal in pernicious anemia. The dose of the liver preparation we employed in these 2 infants contained only about 1.5 to 3.0 micrograms of pteroylglumatic acid per day, an amount which hardly seems sufficient to account for the dramatic results. The small quantity might indicate that this type of megaloblastic anemia arose as a result of a deficiency of erythrocyte maturation factor through a lack of extrinsic or intrinsic factor, rather than because of a deficiency of pteroylglutamic acid.

So far as the intrinsic factor is concerned, it was observed that these 2 infants had no free hydrochloric acid in their gastric contents even after administration of 0.1 mg. histamine per kilogram intramuscularly. Months after the anemia had been treated with liver extract there was an abundance of free hydrochloric acid excreted in the stomach after injection of histamine (equivalent to approximately 30 cc. of tenth-normal sodium hydroxide solution per hundred cubic centimeters of gastric juice in each infant).

Experiments are in progress to determine the role of extrinsic factor as well as the other aforementioned considerations.

Influence of Pteroylglutamic Acid on Tyrosine Metabolism in the Scorbutic Guinea Pig. Dr. Calvin W. Woodruff (by invitation) and Dr. William J. Darby (by invitation), Nashville, Tenn.

Albino guinea pigs weighing about 300 Gm. were placed on a scorbutogenic diet containing 5 per cent *l*-tyrosine. The resulting hydroxyphenyluria disappeared following the administration of 1 to 15 mg. of pteroylglutamic acid daily either subcutaneously or orally. This response was similar to that seen following administration of ascorbic acid. Hydroxyphenyluria could also be prevented by either vitamin. Homogentisic acid was excreted in significant amounts in only 1 of 8 animals studied. These studies suggest that pteroylglutamic acid may play a role in tyrosine metabolism.

Relationship of Anemia and Scurvy. Dr. Wolf W. Zuelzer, Dr. Lucile Hutaff (by invitation) and Dr. Leonard Apt (by invitation), Detroit.

Thirty-six cases of infantile scurvy were studied with the purpose of investigating the relation between vitamin C deficiency and anemia. The criteria for scurvy used were the roentgenologic features of the skeleton, the Kajdi vitamin C indexes, the hematologic studies, including daily blood counts and reticulocyte counts, bone marrow studies before and after treatment, and, in a few cases, serum iron levels. The anemia usually noted in cases of scurvy does not present a uniform picture. Macrocytic, normocytic, normochromic and microcytic hypochromic pictures were observed with corresponding bone marrow patterns. Correlation of the clinical and hematologic features indicated that the anemia found in scurvy represents a variety of mechanisms; namely, (1) response to hemorrhage, (2) infection, (3) coexisting specific deficiencies, such as liver principle deficiency in megaloblastic anemia and iron deficiency. It could be shown that in the presence of continued vitamin C deficiency good hemopoietic responses were obtained with folic acid when the marrow pattern was megaloblastic, but no secondary reticulocyte response following the subsequent administration of vitamin C was noted. Conversely, in the presence of liver principle deficiency, vitamin C alone did not effect a hematologic response until liver or folic acid was given. Similarly, the administration of vitamin C did not cure the anemia when it was of the iron deficiency type.

The results indicate that vitamin C deficiency per se does not lead to anemia and that vitamin C is not a specific hemopoietic factor, contrary to often quoted statements in the literature based on inadequate observations.

Response of Congenital Hypoplastic Anemia to Short Wave Diathermy. Dr. E. N. Nelson (by invitation) and Dr. R. A. Aldrich (by invitation), Minneapolis.

Chronic hypoplastic anemia is characterized by a specific depression or lack of development in the erythroid series without a corresponding diminution of the

granulocytes or platelets, the latter feature differentiating this condition from aplastic anemia.

Some authors regard the disorder as being of congenital origin because it occurs in the early months of life. There is no familial tendency. Infection is probably not an etiologic factor and no endocrine disturbances have been noted. It is thought to represent some error of pigment metabolism or a deficiency in some substance concerned in erythropoietic activity.

The present report deals with the case of a white female infant who was first seen at the University of Minnesota Hospitals in 1945 at the age of 4 months, with a history of pallor, poor appetite, fussiness and sleeplessness. Her hemoglobin concentration and red blood cell counts were low. The platelets were normal. The bone marrow had a depresssion of the erythroid series with cells only in the pronormoblast stage. The granulocytes were normal. There was a slight increase in the eosinophils and a pronounced increase in lymphocytes, some of which looked immature.

She was treated with numerous blood transfusions and by administration of iron and liver orally and liver extract intramuscularly. At one time folic acid was tried in 10 mg. doses. At no time did she respond to these measures with reticulocytosis.

Results of later examination of the bone marrow were similar to those obtained in the first except for the fact that the developing erythroid cells had dropped from 15 per cent to less than 1 per cent and the lymphocytes had increased.

In December 1946, she was started on short wave diathermy therapy. This was given by a pancake coil over her long bones and sternum for fifteen minutes at 100 milliamperes, three times a week. Prompt reticulocyte response was obtained in seven to ten days. The bone marrow returned to normal with 21 per cent of developing erythroid cells. The lymphocytes likewise returned to normal. The child has been maintained exclusively on this therapy during the past sixteen months without blood transfusions. On two occasions when the parents failed to bring the patient for treatment, her hemoglobin concentration and red blood cell count fell again to low levels. With resumption of therapy with diathermy, however, reticulocytosis occurred on each occasion.

The urinary coproporphyrin, urinary and fecal urobilinogen, serum bilirubin and serum iron levels were found to be normal. She had an elevated erythrocyte protoporphyrin content associated with the reticulocytosis.

Effect of Chemotherapeutic Agents on Acute Leukemia; Folic Acid Antagonists. Dr. Sidney Farber, Dr. Louis K. Diamond, Dr. Robert D. Mercer (by invitation), Dr. Robert F. Sylvester (by invitation), Dr. James Wolf (by invitation) and Dr. Gilbert G. Lenz, Boston.

Temporary remissions in the course of acute leukemia in children of a type not hitherto encountered in our experience were described recently by one of us (S. F.). Farber's observation of what he termed an "acceleration phenomenon" in the leukemic process as seen in the marrow and viscera of children with acute leukemia treated by the injection of pteroyltriglutamic acid in 1947, and his earlier observations on the marrow in folic acid deficiency in the rat, led him to the suggestion that folic acid antagonists might be of value in treatment of patients with acute leukemia, with or without pretreatment with folic acid or folic acid conjugates. A series of folic acid antagonists were therefore supplied or synthesized by Dr. Y. Subbarow and his colleagues: James M. Smith Jr., Donna Dean Kosulich, Martin E. Hultquist, Doris S. Seegar, D. L. Hutchins and others. The research of these chemists at the Lederle Laboratories, Inc., Pearl River, N. Y., and the Calco

Chemical Co., Inc., Bound Brook, N. J., made possible our studies on children with acute leukemia.

Farber described the production of temporary and repeated remissions in children with acute leukemia by the administration of folic acid antagonists—pteroylaspartic acid, methylpteroic acid and 4-aminopteroylglutamic acid. The first two substances, studied with the collaboration of Dr. Gilbert Lenz, Dr. James Hawkins, Dr. Robert Mercer, and Dr. E. Converse Peirce, were responsible for slow and moderate changes in the bone marrow and the hematologic picture. The use of 4-aminopteroylglutamic acid ("aminopterin") was followed by the most rapid and satisfactory remissions. These studies on folic acid antagonists opened a promising direction for further research concerning the nature and treatment of acute leukemia in children.

It is the purpose of this paper to supply details of clinical, hematologic and bone marrow studies on a series of children with acute leukemia treated by the intramuscular injection of 4-aminopteroylglutamic acid. Mention is also made of preliminary studies on 17 patients, 10 of whom were children with acute leukemia treated with another folic acid antagonist, 4-methylpteroylglutamic acid ("amethopterin").

Of 16 infants and children with acute leukemia treated with "aminopterin," 10 showed clinical, hematologic and pathologic evidences of improvement of important nature of four months' duration at the time of this report. Six patients did not respond well; 4 of these are now dead, and 2 were unimproved.

These observations show that "aminopterin" has a pronounced effect on the leukemic marrow and on the immature cells in the peripheral blood; judging from the disappearance of the enlargement of the spleen, liver and lymph nodes when such enlargement was present, it also very likely has an effect on leukemic deposits in the viscera as well. During treatment with "aminopterin" the white blood count tended to find a normal level. This tendency occurred in patients in whom the white count was initially high, and also in those who showed severe leukopenia at the onset of the therapy. The percentage of immature cells fell; the blast forms decreased strikingly and in some patients disappeared from the peripheral blood. The relative percentage of mature leukocytes tended to approach normal values in the peripheral blood. Changes included improvement approaching the normal in hemoglobin concentration and red blood cell and platelet counts. Studies of the bone marrow showed changes which varied from decrease in number to disappearance of the leukemic cells and variation from hypoplasia to an almost normal pattern. Toxic effects included stomatitis, with early ulceration. It is impossible to state whether the substance will be of value for a period of time longer than that covered by these studies. The toxic effects may make continued use of the drug impossible.

It is again emphasized that the remissions observed are temporary in character, that the substance is toxic and that it may be productive of even greater disturbances than have been encountered so far in our studies. No evidence has been mentioned in this report which would justify the suggestion of the term "cure" of acute leukemia in children.

Osmotic Resistance of Red Cell Populations in Various Anemias of Infancy and Childhood: Preliminary Observations. Dr. B. Dickstein (by invitation), Dr. I. J. Wolman, Dr. W. E. Love (by invitation), Dr. T. H. Wilson (by invitation) and Dr. W. E. Landmesser (by invitation), Philadelphia.

With use of an existing instrument, the Sanborn "cardiette," suitably modified, more than 1,200 permanent photographic records of the curves for osmotic

hemolysis of 300 samples of normal and abnormal blood from infants and children were obtained. The results were absolutely reproducible, provided attention was paid to (1) p_H, (2) temperature, (3) oxygenation, (4) proportion of cells and solution, (5) rapidity of mixing and (6) length of exposure.

Capillary blood is collected from a finger into 0.9 per cent sodium chloride solution properly buffered with phosphate to a p_H of 7.4. Collection from the finger rather than the vein enhances the value of the test in pediatric practice. The density of the cell suspension is adjusted by diluting it to a red-filter reading of 480 on the Klett photometer. One part of the adjusted suspension and four parts of the hemolytic solution are brought to 24 C. (75 F.) and suddenly mixed.

Four hemolytic solutions were employed for each sample of blood tested, namely, 0.36 per cent sodium chloride solution, 0.47 per cent sodium chloride solution, a mixture containing 0.36 per cent sodium chloride and 0.18 mol glycerin U. S. P. and one containing 0.18 per cent sodium chloride and 0.24 mol thiourea. All tests were done within four hours of collection. In the preparation of the salt solution silver-free sodium chloride was used. For the glycerin test, distilled water prepared in glass or block tin rather than copper containers was used. Traces of copper inhibit the special mechanism by which glycerin penetrates the red cell.

The red cells in normal children in the first fifteen years of life showed greater osmotic resistance than those of adults. Hence adult controls cannot be used for fragility studies in infancy and childhood.

The red cells of 75 normal Negroes (without sickle cell anemia) when compared with blood from 75 normal white persons showed greater variations in fragility and on the average were more resistant than those of the white persons. This confirms the work of Helm and Jacobs. Ten normal Chinese followed the resistance pattern of the normal white persons.

The red cells of a group of 30 patients with sickle cell anemia presented considerably more osmotic resistance than those of the normal Negro. Increased resistance of the red cells was noted in the apparently healthy members of families in which the sickling tendency was present.

Ten cases of familial erythroblastic (Cooley's) anemia and 19 cases of the mild disease or carrier state all showed increased osmotic resistance, resistance in the carrier state being as great as, or greater than, that in the mild state. The increased resistance makes this an exceedingly important test in the detection of the carrier state and a valuable tool in genetic studies.

The method is especially sensitive in detecting slight alterations in fragility.

There is no direct correlation between anemia and osmotic resistance in anemic patients. In normal persons all degrees of resistance may exist at a fixed hemoglobin level.

Mechanism of the Sickling Phenomenon. Dr. Chandler Stetson Jr. (by invitation) and Dr. Lewis Thomas, Baltimore.

The effect of several reducing agents on the red cells of patients with sickle cell disease was studied. In the case of hydrogen sulfide, BAL and cysteine, sickling was produced with such promptness and regularity that the method is suitable for routine diagnostic use. With suitable concentrations of these agents, sickling is usually apparent within five to ten minutes and reaches a maximum within twenty to thirty minutes. Other reagents, such as ascorbic acid, glutathione, pyrogallol and sodium bisulfite require a somewhat longer time for their action.

The hypothesis is offered that sulfhydril compounds may play an important role in spontaneous sickling. This concept is supported by the observation that spontaneous sickling is definitely inhibited by such thiol antagonists as quinone, hydro-

quinone, iodosobenzoate, o-chloromercuribenzoate, iodoacetate and certain heavy metal ions.

The addition of small amounts of hydrogen sulfide or BAL to samples of blood from patients with sickle cell disease results in a pronounced decrease in the sedimentation rate of the erythrocytes, with a concomitant increase in the hematocrit. These phenomena are correlated with the production of sickling in the treated samples of blood and with a change from oxyhemoglobin to reduced hemoglobin, observed spectroscopically.

Examinations of sickled cells with the aid of the electron microscope, with polarized light and with the x-ray diffraction technic have thus far failed to support the hypothesis that sickling is accompanied with the formation of intracellular crystals of hemoglobin.

Myotonia Congenita, Experimental Study. Dr. Donald R. Hirsch (by invitation), Dr. Richard S. Ward (by invitation) and Dr. Joseph Dancis (by invitation), New York.

A 6 year old Negro boy with myotonia congenita (Thomsen's disease) was studied. Motion pictures were taken demonstrating the clinical characteristics of the condition. In order better to localize the site of pathologic lesions in myotonia, the effect of curare on the myotonic reaction was investigated. In spite of curarization to the point of diaphragmatic paralysis, the myotonic response could still be elicited mechanically. This indicates that the pathologic change is distal to the point of action of curare, which is thought to be at the end plate or distal to it. Since veratrine reproduces the myotonic phenomenon in normal muscle in vitro, a search was made for a veratrine-like substance in this patient's blood. Blood was withdrawn during rest, after strenuous effort and following application of a tourniquet. This was tested according to the method of Löwi. No veratrine-like substance could be demonstrated.

Balance and Electrocardiographic Studies in Potassium Deficiency. Dr. William M. Wallace and Dr. Frederic C. Moll (by invitation), Boston.

The patient was a 4 year old boy born with extrophy of the bladder. At 3½ years of age pyelograms showed bilateral hydroureters and pelves. Transplantation of the ureters into the sigmoid was done at this time. Four months later fever, vomiting and severe diarrhea developed, and he was brought to the hospital in a dehydrated, acidotic state. For two days he was treated with large volumes of isotonic sodium chloride, and glucose solutions, plasma and some whole blood. With chemotherapy and parenteral administration of fluids the fever subsided and hydration improved. However, with the improvement severe muscular weakness developed and on the third day became alarming. Clinical diagnosis of potassium deficiency was made and substantiated by the serum potassium level of 0.75 millimol per liter. The electrocardiogram showed a rate of 140, a normal PR interval but a prolonged QT interval. The QRS interval was in the upper limit of normal. There was prominent depression of the ST take-off and the T wave was diphasic.

The child was placed on a metabolism bed. In a period of four hours, initially, 525 cc. of the solution containing potassium described by Darrow was given intravenously. Serial electrocardiograms demonstrated an immediate drop in rate and a striking improvement in the ST take-off when only 125 cc. of the solution had been given at the end of the first hour. At this time the serum potassium level was only 1.2 millimol per liter. Return of muscular strength was complete in four hours.

During the first twenty-four hours, the electrocardiogram returned to nearly normal, although the serum potassium level was only 1.8 millimol per liter. The level rose to 3.8 millimols on the third day of the study, accompanied with only minor changes in the electrocardiogram.

Consideration of the balance studies showed almost quantitative retention of potassium administered, amounting to 10 millimols per kilogram in the face of a negative nitrogen balance. The amount lost in the urine was small. On the first day when parenteral therapy was given, the balance of sodium and chloride was strongly positive because of the large amounts of these extracellular ions administered. During the last three days, when the child was receiving a relatively normal diet orally, one in which the potassium exceeded the sodium and chloride, the sodium balance became negative and the chloride balance was stationary.

Our interpretation of the sequence of events is as follows:

Pronounced potassium deficiency occurred as a result of the lack of intake and the diarrhea. Rehydration with large amounts of saline and glucose solutions caused further reduction in potassium concentration. That a renal defect in resorption of potassium could have played a part seems unlikely in view of the excellent conservation of potassium by the kidney in the repair period. When an intake of potassium was provided, this ion was almost quantitatively retained. Concomitantly, some sodium was lost from the cells. The direction of the balance would seem to indicate that this process was continuing when the study was stopped. The clinical symptoms, electrocardiographic reading and the lack of correlation between these and the serum level have been previously described by others. The latter descriptions led some investigators to the surmise that cellular potassium content, rather than extracellular levels, determine the appearance of symptoms. During the four day period, this patient retained approximately 10 millimols of potassium per kilogram, or about 16 per cent of the expected body content of the ion. However, symptoms disappeared when only a small fraction of this amount had been given.

Apparently, in this instance, neither the extracellular nor the intracellular content of potassium was the critical factor. It is perhaps permissible to suggest that the astonishingly rapid therapeutic effect of the administered potassium may have been produced by a concentration at cell surfaces during the process of passage into the cell fluid.

Mineral Metabolism in Rats with Alloxan-Induced Diabetes. Dr. William A. Brodsky (by invitation), Dr. Norton Nelson (by invitation) and Dr. George M. Guest, Cincinnati.

The purpose of this study was to obtain a precise quantitation of mineral exchange in diabetic animals under rigidly controlled conditions such as could not be imposed with human subjects. Therefore, balance studies were conducted on rats during periods of normal control, fasting, development of diabetes after administration of alloxan, diabetic states controlled with insulin, development of and recovery from acidosis and fatal acidosis. Data obtained included determinations of sodium, potassium, calcium, chloride, phosphorus, nitrogen and glucose.

After a twenty-four hour fast, rats were given intravenous injections with alloxan in doses of 50 mg. per kilogram of body weight. Severe diabetes developed in each of them. Injections of protamine zinc-insulin in doses of 1 to 1½ units daily resulted in maintenance of body weight with mineral equilibrium. Glycosuria amounted to 0.5 to 2 Gm. of glucose per day.

The food intake varied after insulin was withdrawn. Rats which continued to eat the same amount of food showed only slight loss in weight and mineral

equilibrium was maintained despite increased glycosuria. When the food intake fell during insulin deprivation, dramatic losses in weight and large negative mineral balances resulted. Death occurred within two to four days after withdrawal of insulin.

Some rats consumed food in amounts exceeding their previous control intakes during insulin deprivation. These animals survived for as long as two and one-half to four weeks, despite gross polyuria and excretion of as much as 10 Gm. of glucose daily. Excretion of acetone ceased when the rats began to overeat. However, body weights fell steadily throughout the entire period, and the nitrogen balances remained negative.

Estimates of the loss of body fluid incurred during a period of fatal acidosis showed the following facts: In two to three days, the animals lost 20 to 25 per cent of their body weight. The loss of extracellular fluid calculated from the sodium balances amounted to 22 to 27 per cent of the estimated extracellular space. Protoplasmic loss, calculated from the nitrogen balances, was 11 to 21 Gm. Potassium was lost in excess of nitrogen, and the excess accounted for 10 to 17 Gm. of intracellular fluid. The loss of intracellular fluid was 15 to 25 per cent of the estimated intracellular compartment. These estimates accounted for 80 per cent of the actual losses in weight.

After resumption of insulin therapy in acidotic rats, mineral balances followed a characteristic pattern. In the first two to three days, retentions actually exceeded the losses that occurred during acidosis. Eventually, in the fifth to sixth day of the postacidotic period losses of minerals were observed prior to the attainment of a state of equilibrium.

Book Reviews

Psychopathology and Education of the Brain-Injured Child. By A. A. Strauss and L. E. Lehtinen. Price, $5. Pp. 206, with illustrations. New York: Grune & Stratton, Inc., 1947.

This thoroughgoing study of the difficulties experienced by children with cortical injury on encountering ordinary educational and social experiences is also an account of concessions in the usual curriculum which have made learning easier for them. The authors' orientation is primarily psychologic and educational, and no extensive medical discussion is attempted. Previous work along psychologic lines is reviewed, and, in addition, the book is rich in references to the relevant literature.

The fundamental thesis of the book is that the cortex, or, as the authors refer to it, the new brain, acts as an inhibitive and correlative mechanism controlling and organizing the otherwise disinhibited activity of the lower centers. While injury to specific areas of the cortex may produce specialized changes in function, local in their cortical representation, generalized changes in the perceptual, thinking and behavioral fields are also produced. Since growth and development may compensate for local effects of lesions occurring early in life, the characteristic social and educational dislocations are the result of the generalized disturbances of cortical function.

Methods of exploring and defining perceptual and thinking aberrations and their bearing on conduct and education are discussed in the first half of the book. Comparisons are made between thinking processes of children with congenital (endogenous) defects and those with injury to the brain (exogenous defects). Behavior in the circumstances under which the children were observed is also discussed and classified, though it does not seem to me necessarily true that the behavior would run true to type in other circumstances.

Fundamentally, similar methods of psychologic examination have been used in many clinics to determine organic brain damage, and their validity as an evidence of cortical injury is unquestioned. In many instances, such psychologic observations have given the first hint of unsuspected brain diseases.

The second section, dealing with educational methods, is, as far as I know, the first attempt to present an organized program for the education of these unfortunate children. It seems soundly conceived and, judging by the results stated to have been achieved, must have validity. Great patience and ingenuity have gone into its elaboration, and the authors would unquestionably be the last to consider it a finished program. If in the hands of others similar success can be achieved, great strides in teaching brain-injured children the fundamental educational technics are outlined. It remains to be seen how well this addition to the education of brain-injured children will allow them to compete.

The book is an important contribution, and its contents should be part of the equipment of all who deal either medically or educationally with children with diseases of or damage to the brain.

The Foot and Ankle: Their Injuries, Diseases, Deformities and Disabilities. Third edition. By Philip Lewin, M.D., F.A.C.S. Price, $11. Pp. 847, with 389 illustrations. Philadelphia: Lea & Febiger, 1947.

This book contains an amazing amount of information in detail so complete that it should prove an invaluable reference guide to many physicians other than orthopedists. Many varieties of surgical technic, with generous references to the

works of other writers, make it an indispensable item to the worker in any field whose duties call for knowledge of the feet.

The pediatrician's interest is largely in the comments which help answer perplexing questions regarding foot care and shoes for growing children and give a basis for authoritative opinions on subjects which are still controversial among orthopedists.

On these items the author is explicit: The tendency has been away from rigid supports, and many feel that raising the inner border of the heel is sufficient to invert the calcaneus. The weight of the shoe is rarely an important consideration; this is especially true in young children for whom a sturdy shoe is desirable. The function of the shoe is to protect against hardness and unevenness of the ground and against cold and to provide support and determine locomotion: it should be narrow in the heel and through the waist of the foot but wide through the ball.

Children should be allowed to go barefoot only in the sand or on soft surfaces and should be instructed to toe in. Counterless shoes and loafers offer no support and are bad. Gymnasium and ballet shoes should be worn only for their intended purposes. Particularly during convalescence, the feet should be supported at all times and bedroom slippers never permitted.

Kiddie cars may cause knock knee and flatfoot.

The possibility of short sox and short shoes should be kept constantly in mind. If the nail beds are red and tender on back pressure, it means too short shoes.

Dr. Lewin warns against belly sleeping and harmful sitting postures, such as legs folded under until the feet touch the buttocks which results in damage to knee ligaments, bowed legs and pigeon toes.

Roller skating and ballet dancing are especially recommended.

The author prefers to correct congenital defects such as clubfoot within a few hours after birth. He gives his own method and discusses the nonsurgical methods, such as the Denis-Browne splints, Kite's wedge plaster method, and the use of the Sabel shoes.

Overriding and underriding toes are common congenital defects. If treated immediately by strapping, and the treatment is persisted in, practically all cases can be cured.

Active exercises are the keys to cure or correction of pronated feet in children. Leg cramps in children at night may be due to pronated feet.

Short paragraphs called "Pedigrams" close the book; among those of interest to pediatricians are the following:

> When your ankle rolls in your troubles begin.
> The height of the arch does not determine the usefulness of the feet.
> A flexible shoe is sufficient for those who need only exercise, but for those who need also support a rigid shank shoe is necessary.

Child and Adolescent Life in Health and Disease. Edited by W. S. Craig, M.D., F.R.C.P.E., F.R.S.E. Price $7. Pp 600, with illustrations. Baltimore: William & Wilkins Company, 1946.

The title of this book may mislead American readers, for this is not another pediatric textbook but the story of the development of health and welfare work in England, written in an exceedingly interesting style. In its 600 pages, the author succeeds so well in selecting the significant events that in its sphere it gives as satisfactory a picture of the subject as does a good stage production of a complete novel.

The book is devoted to the history of the legislation regarding child welfare, the development of pediatrics as a specialty and the growth of public and private agencies. It has even a chapter on children in wartime, giving the story of the

evacuation. The book is generously illustrated with old prints, pictures, paintings and illustrations of early textbooks. Some 100 pages are devoted to legislation. The appendix lists hospitals and children's institutions in England by size and age group of patients accommodated; finally, there is a chronologic list of significant events and periods in the development of the child health and welfare services.

The author states, "The present day picture of the provision for the care of child life and health can be compared to an unfinished jigsaw puzzle. Each piece of the puzzle has its own historical background. Many have been pieced together to form a recognizable part of the picture. The puzzle has not, however, been completed. Isolated pieces remain to be properly placed. Others have been dubiously inserted. Some are missing." This paragraph reflects also the viewpoint of the American Academy of Pediatrics in regard to the situation of child health in the United States. This viewpoint motivated the appointment, first, of the committee for the study of child health services and, then, that of the one on the improvement of child health care. In fact, a similar story of the historical background of legislation, pediatrics and private health and welfare agencies in the United States would seem especially unappropriate at this time. The book should be familiar to every pediatrician, and it will most assuredly interest many other physicians and public health and welfare workers.

Motivation in Health Education: The New York Academy of Medicine, Health Education Conference, 1947. Price, $1. Pp. 53, with no illustrations. New York: Columbia University Press, 1948.

This small volume is an excellent treatise defining the problem of motivation in health education. For the reader who is looking for a simple formula, there is disappointment.

Iago Galdston, M.D., gives a historical background for health education, with sufficient reference to religion and philosophy "to awaken a realization that health education is not a pursuit in 'splendid isolation.'"

W. W. Bauer, M.D., describes a more recent picture, with interesting comments on the changing concepts concerning tight corseting, cigaret smoking, venereal disease crusades, graham flour, fear motivation and others, and then turns to the "refinement" and "social éclat" in the modern era of health education. He points to "the rise of the orange from a luxury fruit . . . to its present status of a *must* in every diet," not as "an awakened appreciation of the vitamin C and calcium values in the orange" and not from a motivation of fear. He warns that "health education attracts neurotics" and motivation "is not simple," and adds, "What we must do is to utilize every motivation to the best possible advantage."

Lawrence S. Kirbie, M.D., with the fascinating revelations of the psychiatrist concerning inner psychologic forces, points out the myths and resistances to real health education. To overcome these psychologic obstacles, he predicts "will require many years of thought and effort."

The anthropologist, Margaret Mead, offers the most constructive suggestions as to how the job can be done in her chapter, "Positive Motivations in Health Education." She draws from "The Problem of Changing Food Habits," (National Research Council Bulletin No. 108, 1943) and other applications of anthropologic methods. She points out that successful advertisers have turned away from the self-defeating advertising that stressed what is "good-for-you." She refers to "the citrus fruit advertisement which showed a little girl who winks as she drinks her orange juice, with the caption, 'I'm glad I *need* orange juice.'" Here the aim is to shift orange juice away from the "good-for-you" class into the "good" class and still deal indirectly with the "good-for-you" theme.

The Baby's First Two Years. By Richard M. Smith, M.D. Price, $2.75. Pp. 181, with 15 illustrations. Boston: Houghton Mifflin Company, 1948.

Dr. Smith's book is in its fifth edition, which speaks well for its usefulness to the new mother. Certainly it stands out as an exception to the vast majority of books of this type which are now being published. The routine advice on feeding, training and habits is what one would expect from a man of Dr. Smith's experience. A brief chapter on sickness is a model of calm, common sense advise. A section on the new mother answers many of the problems with which she is confronted. The schedule of a baby's typical day, if read carefully, would save many a question. The section on recipes could well be omitted, since most of the preparations are available commercially.

This book is far above most of its type. It can be recommended for most new mothers.

Widening Horizons in Medical Education: A Study of the Teaching of Social and Environmental Factors in Medicine, 1945-1946. Report of the Joint Committee of the Association of American Medical Colleges and the American Association of Medical Social Workers. Price, $2.75. Pp. 228, with no illustrations. New York: The Commonwealth Fund, Division of Publications, 1948.

This is the report of the survey on the instruction in social and environmental factors in medicine given by the various medical schools in the Association of American Medical Colleges. The committee submitting the report represented both the Association of American Medical Colleges and the American Association of Medical Social Workers.

It is apparent that social and environmental factors in medicine have not been uniformly recognized in the curriculums of the several schools. There is apparently a tendency to relegate social factors to departments of social service and to overlook the importance of those factors in the individual patient. Perhaps the increasing emphasis on metabolic tests and physiopathologic studies has crowded out the consideration by the physician of social and environmental factors.

In any event, it would seem that the role of sociology in medicine should not, cannot, be relegated entirely to social service or to public health personnel but should be constantly integrated with the problem of sickness in the individual patient. With that premise it is obvious that the teachers of medicine must themselves be sympathetic and willing to bring to the attention of their students the social and environmental factors.

As might be expected, there are wide variations in the manner or method by which social and environmental factors in medicine are presented to medical students. From some schools, one gets the impression that there is considerable indifference on the part of faculties; in other schools there seem to be didactic lecture programs; while in another type of school, the sociologic aspects are considered the area of the social worker, as a separate profession.

At Massachusetts General Hospital, Boston, the participation of the clinicians appears well established. The family health adviser project at Cornell University Medical College, New York, allows for a long term social observation by the student. The University of Pennsylvania School of Medicine presents the social phase of medicine through the social worker with apparently no clinician participating.

The ideal at present seems to be that curriculum which brings to the student the recognition of social factors by both medical faculty and social service. This

presupposes a faculty in medicine the members of which are themselves adequately informed regarding social changes and who are thus able to use properly the services of the professional social worker in relation to the patient. It is apparent that not all faculties are so informed.

The Contemporary American Family. By Ernest R. Groves and Gladys Hoagland Groves. Price, $4.50. Pp. 838. Philadelphia: J. B. Lippincott Company, 1947.

This book is a completely rewritten and reset edition of the authors' earlier work in 1934, "The American Family," and clearly reflects the more recent developments in sociologic thinking in this field. Drawing largely on this previous work, the authors give the reader an insight and preparedness that will help him handle his own problems, whether they are associated with premarriage, marriage or parenthood experiences. In accomplishing this purpose, the Groves' study is divided into four parts giving the development of the American family and the significance of the family as a social institution (part I), the emotional and psychologic aspects of our present domestic manner of life (part II), the important social problems associated with American family life (part III) and the resources available for the improvement and strengthening of family life, emphasizing the interests of the family as a social organization and the potential values of marriage and parenthood for the individual person (part IV).

The chapter on "The Medical Approach" brings out the manner in which medicine in both its preventive and its curative aspects affects family life in a multitude of ways. No application of science to human need has contributed more to the welfare of the family than preventive medicine. As the student considers the specific advances medicine has made in ministering to the problems relating to marriage and family experience, it is most important to remember that the progress made is cumulative, each accomplishment becoming an incentive for still greater advance.

Past conquests have changed the spirit of medicine and prepared it for the new social program that must come in response to family need and pressure, especially within the middle class. When one takes into account the character of its responsibilities and its opportunities for exploitation, medicine as a profession has a code of ethics unexcelled. The American physician believes these standards would quickly be undermined if the practice of medicine came under the control of either the state or the federal government, thereby becoming subject to political manipulation and pressure. In the opinion of the authors, the resources of modern medicine must be made more available to the middle class. If the members of the profession refuse to help work out a program that will conserve the interests of both the physician and the general public, government control may result. While Congress debates plans for medical care for the American people, millions of free-thinking Americans are quietly joining together to get low cost medical protection under the age-old system for which America is famous, the voluntary system. It does not attempt to provide complete medical coverage. It is seeking to "walk toward" a partial and practical solution—first, taking care of catastrophes and, then, as the people themselves become more educated to their needs, gradually unfolding into a more elaborate program.

This revision, so well supplemented with literary and bibliographic appendixes, will find wide acceptance not only by the student interested in gaining a clearer concept of his own personal problems but also by the young physician as excellent background material in his professional work of extending the best health and medical service to the American family.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

Sixth International Congress of Pediatrics

President: Prof. Guido Fanconi.
American Committee:
President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. S. G. Ross, 1390 Sherbrooke St. W., Montreal.
Place: Zurich, Switzerland. Time: July 24-28, 1950.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Pan American Congress of Pediatrics

President: Dr. Felix Hurtado, Habana, Cuba.

International Union for Child Welfare

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secçaõ de Pediatrias

President: Dr. Armando de Arruda Sampaio.
First Secretary: Dr. Luis Fontoura y Lauro Machado Oliveira, Caixa Postal 2103, São Paulo, Brazil.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Society

President: Dr. H. T. Ashby, 13 St. John St., Manchester, England.
Joint Secretary: Prof. Alan Moncrieff, Hospital for Sick Children, Great Ormond St., London W. C. 1.
Place: Windermere.

Chinese Pediatric Society

President: Dr. W. S. Fu, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Secretary: Dr. T. F. Su, The Shanghai Public Hospital for Children, 11 Hsiang Shan Road, Shanghai, China.
Time: Concurrent with the annual conference of the Chinese Medical Association.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Danish Pediatric Society

President: Prof. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandsche Vereeniging voor Kindergeneeskunde

President: Dr. J. L. Keyzer, 114 St. Josephstr., Tilburg.
Secretary: Dr. H. Reerkink, % Sophia Kinderziekenhuis, 160 Gordelweg, Rotterdam.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. L. F. Meyer, 29 Toelsohn St. Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

Royal Society of Medicine, Section for the Study of Diseases in Children

President: Prof. J. M. Smellie, 5 Flat, 8 Bolingbroke Grove, London S. W. 11.
Secretary: Dr. Mary Wilmers; Dr. R. Bonham Carter.
Place: 1 Wimpole St., London W. 1. Time: Fourth Friday of each month, 4:15 p. m.

Schweizerische Gesellschaft für Pädiatrie

President: Prof. Dr. A. Hottinger, Petersplatz 12, Basel.
Secretary: Dr. F. Hauser, Kinderspital, Basel.

Sociedad Boliviana de Pediatria

President: Dr. Carlos Ferrufino, Casilla 272, La Paz, Bolivia.
Secretary: Dr. Cecilio Abela Deheza, Bolivia.
Place: S. C. I. S. P. Bldg. Time: Every Thursday.

Sociedad Chilena de Pediatria

President: Mr. Raúl Matte, Santiago, Chile.
General Secretary: Dr. Mariano Latorre, Santiago, Chile.
Place: Medical Society, Santiago, Chile. Time: 7:30 p. m., weekly.

Sociedad Cubana de Pediatria

President: Prof. Agustin Castellanos.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: 9 p. m., last Wednesday of every month.

Sociedad Dominicana de Pediatria

President: Dr. Alberto Peguero, Avenida Bolivar 117, Ciudad Trujillo, R.D.
Secretary-Treasurer: Dr. Jaime Jorge, Lea de Castro 19, Ciudad Trujillo, R.D.
Place: Children's Ramfis Hospital. Time: 8 p. m., last Friday of every month.

Sociedad Ecuatoriana de Pediatria

President: Dr. Alfredo Ceballos Carrión.
Secretary: Dr. Rafael Compte Andrade, P. O. Box 3480, Guayaquil.
Place: Hospital Central. Time: 11:30 a. m., every Friday.

Sociedad Mexicana de Pediatria

President: Dr. Jesus Avarez de los Cobos.
Secretary: Dr. Luis Torregrosa F.
Place: Hospital Infantil. Time: Last Thursday of every month.

SOCIEDAD DE PEDIATRÍA DE CONCEPCIÓN (CHILE)

President: Dr. Raúl Ortega A., Hospital Clínico Regional, Concepción.
Secretary: Dr. Fidel Urrutia, Hospital Clínico Regional, Concepción.
Place: Hospital Clínico Regional, Concepción. Time: 7:30 p. m., Second Tuesday of every month from April to December, inclusive.

SOCIEDAD DE PEDIATRÍA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Albino F. Dottori, Dean Fumes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Fumes 2000, Córdoba, Argentina.
Time: Once a month.

SOCIEDAD DE PEDIATRIA DEL LITORAL

President: Dr. Jose E. Celoria, Hospital Centenario, Rosario, Argentina.
Secretary: Dr. Gloria Lovell, Hospital Centenario, Rosario, Argentina.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pastor Oropeza, Caracas.
Secretary: Dr. Guillermo Flores, Chacin, Sur 17, no. 26-2, Caracas.
Place: Hospital Municipal de Niños, Caracas. Time: Once a Month.

SOCIEDAD YUCATECA DE PEDIATRIA

President: Dr. José Lavalle, Yucatan, Mexico.
Secretary: Dr. Francisco Solís, Yucatan, Mexico.
Place: Hospital del Niño, Yucatan, Mexico.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. G. Heuyer, 1 Ave. Emile Deschanel, Paris 7e, France.
Secretary: Dr. Maurice Lamy, 94 rue de Varenne, Paris 7e, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SOUTH AFRICAN PAEDIATRIC ASSOCIATION

Chairman: Dr. Basil Melle, 89 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.
Secretary-Treasurer: Dr. Seymour Heymann, 17 Lister Bldg., 195 Jeppe St., Johannesburg, South Africa.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Dr. R. Hybbinette, Kommendorsgatan 3, Stockholm.
Secretary: Dr. B. Broman, Eriksbergsgatan 1A, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Héctor C. Bazzano.
Secretary: Dr. José M. Portillo.
Place: Club Medico del Uruguay, Avenda Agraciada 1464 (Piso 13), Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Woodruff L. Crawford, 321 W. State St., Rockford, Ill.
Secretary: Dr. Margaret Mary Nicholson, 1801 Eye St. N. W., Washington, D. C.
Place: Atlantic City, N. J. Time: June 6-10, 1949.

American Academy of Pediatrics

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston 15.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Atlanta, Ga. Time: April 13-15, 1949.
Annual Meeting: Place: San Francisco. Time: Nov. 14-17, 1949.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.

American Pediatric Society

President: Dr. Valjean Cooke, 8700 Argyle Ave., St. Louis.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Atlantic City. Time: May 3-5 (?), 1949.

Canadian Society for the Study of Diseases of Children

President: Dr. P. E. Williams, 193 James St. S., Hamilton, Ontario.
Secretary-Treasurer: Dr. R. L. Denton, 1615 Cedar Ave., Montreal.

Society for Pediatric Research

President: Dr. Sidney Farber, 300 Longwood Ave., Boston.
Secretary: Dr. Robert Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Spencer Snow, 75 S. Main St., Salt Lake City.
Secretary-Treasurer: Dr. Esther Gross, 202 E. South Temple St., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month. 8 p. m.

New England Pediatric Society

President: Dr. Howard W. Brayton, 179 Allyn Street, Hartford 3, Conn.
Secretary-Treasurer: Dr. Harry Shwachman, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Clarence L. Lyon, 407 Riverside Ave., Spokane 8, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.

Northwestern Pediatric Society

President: Dr. Paul Bancroft, 909 Sharp Bldg., Lincoln, Neb.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Rocky Mountain Pediatric Society

President: Dr. John M. Nelson, 1558 Humboldt St., Denver.
Secretary: Dr. Edwin T. Williams, 1850 Gilpin St., Denver 6.
Place: Children's Hospital of the Colorado General Hospital. Time: Monthly from October to June.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Carroll M. Pounders, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.

STATE

Alabama Pediatric Society

President: Dr. W. A. Daniel Jr., 115 S. Union St., Montgomery 5, Ala.
Secretary-Treasurer: Dr. D. B. Monsky, 905 Norman Bridge Rd., Montgomery 6, Ala.
Place: Montgomery, Ala. Time: September 1949

ARIZONA PEDIATRIC SOCIETY

President: Dr. Hugh Thompson Jr., 110 S. Scott St., Tucson, Ariz.
Secretary: Dr. James R. Sickler, Physicians Bldg., Tucson, Ariz.
Place: Phoenix or Tucson. Time: On call.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Alice Potter, 1418 Ninth Ave., San Francisco 22.
Secretary: Dr. Carl Erickson, 595 E. Colorado, Pasadena.
Place: Los Angeles. Time: April 1949.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Edgar W. Stephens, 910 Harvey Bldg., West Palm Beach.
Secretary: Dr. Hugh A. Carithers, 2000 Park St., Jacksonville 4.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Lee Bivings, 20 Fourth St. N. W., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. H. L. F. Locke, 179 Allyn St., Hartford, Conn.
Secretary: Dr. L. W. Minor, 119 Main St., Middletown, Conn.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Eugene T. McEnery, 4458 W. Madison St., Chicago 24.
Secretary: Dr. George L. Drennen, Jacksonville, Ill.
Place: Palmer House, Chicago. Time: May 10-12, 1949.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Charlotte Fisk, 1201 Equitable Bldg., Des Moines 9.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bdg., Davenport.
Place: Des Moines. Time: April 1949.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. William C. Rivenbank, 1448 Louisiana Ave., New Orleans 15.
Secretary-Treasurer: Dr. Bertha Wexler, 3439 Prytania St., New Orleans 15.
Place: New Orleans. Time: May 7, 1949.

MEDICAL SOCIETY OF THE STATE OF NEW YORK, PEDIATRIC SECTION

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Waldo E. Nelson, Temple University, Philadelphia 40.
Secretary: Dr. Carl C. Fischer, 100 W. Coulter St., Philadelphia 44.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. H. J. Lewis, 2956 Biddle Ave., Wyandotte.
Secretary: Dr. Robert H. Trimby, 122 W. Hillsdale, Lansing.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Place, Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. George Clark, 1817 Vinton St., Omaha.
Secretary-Treasurer: Dr. Michael Crofoot, 1407 Medical Arts Bldg., Omaha 2.
Place: Children's Memorial Hospital. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Jersey Medical Society, Pediatric Section

Chairman: Dr. Robert E. Jennings, 117 Washington St., East Orange.
Secretary: Dr. Israel J. Wolf, 231 E. 31st St., Paterson.

New Mexico State Pediatric Society

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

North Carolina Pediatric Society

President: Dr. Samuel F. Ravenel, 371 N. Elm St., Greensboro, N. C.
Secretary: Dr. Charles H. Gay, 1523 Elizabeth Ave., Charlotte, N. C.

Northern California Pediatric Society

President: Dr. William C. Deamer, 3 Fifth Ave., San Francisco 18.
Secretary: Dr. A. L. Gleason, 1066 Longridge Rd., Oakland 10.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

Oklahoma State Pediatric Society

President: Dr. J. B. Snow, 625 N. W. 10th St., Oklahoma City.
Secretary: Dr. Bertha Levy, 1200 N. Walker St., Oklahoma City.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

Philippine Pediatric Society

President: Dr. Alberto V. Tupas, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Secretary: Dr. Artemio P. Jongco, Department of Pediatrics, College of Medicine, University of the Philippines, Manila, Philippines.
Place: Philippine General Hospital. Time: Every two months.

South Carolina Pediatric Society

President: Dr. B. Owen Ravenel, 95 Rutledge Ave., Charleston 16.
Secretary-Treasurer: Dr. John R. Harvin, 206 N. Sumter St., Sumter.

Tennessee Pediatric Society

President: Dr. W. O. Vaughan, 2103 Hayes St., Nashville 5.
Secretary-Treasurer: Dr. C. Barton Etter, 1678 Peach, Memphis 12.
Place: Chattanooga. Time: Second Monday in April.

Texas Pediatric Society

President: Dr. John K. Glen, 4412 Montrose St., Houston.
Secretary-Treasurer: Dr. James N. Walker, 3616 Tulsa Way, Fort Worth 7.
Place: San Antonio. Time: Oct. 7-8, 1949.

Virginia Pediatric Society

President: Dr. C. P. Brown, 142 W. York St., Norfolk.
Secretary: Dr. E. Berkeley Neal, 303 Washington Ave. S. W., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Thomas G. Folsom, 1139 Fourth Ave., Huntington.
Secretary: Dr. Warren J. Parsons, 425 Eleventh St., Huntington.

Wisconsin State Medical Society, Section on Pediatrics

Chairman: Dr. M. G. Peterman, 411 E. Mason St., Milwaukee 2.
Secretary: Dr. L. M. Simonson, 1001 N. 8th St., Sheboygan.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. John Hart Davis, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Francis F. Silver, 9400 Euclid Ave., Cleveland.
Place: Allen Memorial Medical Library. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. A. L. Chute, 170 St. George St., Toronto, Canada.
Secretary: Dr. John Fletcher, 262 St. Clair St. W., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Baltimore City Medical Society, Pediatric Section

Chairman: Dr. Charles O'Donovan Jr., 5 E. Read St., Baltimore .
Secretary: Dr. T. Campbell Goodwin, 16 E. Biddle St., Baltimore.

Bronx Pediatric Society

President: Dr. Harry S. Pizer, 1726 Davidson Ave., New York.
Secretary: Dr. William A. Schonfeld, 211 W. 106th St., New York 25.
Place: Morrisania City Hospital. Time: 8:30 p. m., second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Harold T. Vogel, 3420–86th St., Jackson Heights, N. Y.
Secretary: Dr. Bernard Benjamin, 845 Park Pl., Brooklyn 16.
Place: Granada Hotel. Time: 8:45 p. m., fourth Wednesday of February, March, April, October and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. T. Wood Clarke, 7 Cottage Place, Utica.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. John L. Reichert, 1791 Howard St., Chicago 26.
Secretary: Dr. Alvah L. Newcomb, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati.
Secretary: Dr. William F. Hunting, 6048 Montgomery, Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. Guy Hacker, 5711 Goliad St., Dallas.
Secretary-Treasurer: Dr. George R. Branch, 4325 Cole Ave., Dallas.
Place: Children's Hospital of Texas and Bradford Memorial Hospital. Time: 1 p. m., third Saturday and 8:30 p. m., the first Tuesday of each month.

Detroit Pediatric Society

President: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2.
Secretary: Dr. S. S. Bernstein, 650 Maccabees Bldg., Detroit.
Place: Variable. Time: Five times annually.

Fort Worth Pediatric Society

President: Dr. Frank Cohen, 712 S. Henderson, Fort Worth, Texas.
Secretary: Dr. H. H. Womack, 1422 Pennsylvania, Fort Worth, Texas.
Place: Welch and West Restaurant. Time: Third Friday of each month.

Honolulu Pediatric Society

President: Dr. Donald Marshall, Medical Group, Honolulu.
Secretary-Treasurer: Dr. Teruo Yoshina, 1221 Victoria St., Honolulu

Houston Pediatric Society

President: Dr. Edward O. Fitch, 3720 Fannin St., Houston, Texas.
Secretary: Dr. Thomas J. Donovan, 3506 Sunset Blvd., Houston 5, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., last Tuesday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Hoel Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Knoxville-Oak Ridge Pediatric Society

President: Dr. Henry S. Christian, 205 Medical Arts Bldg., Knoxville, Tenn.
Secretary: Dr. John Eggleston, Oak Ridge Hospital, Oak Ridge, Tenn.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Secretary-Treasurer: Dr. Robert Simonds, 267 S. Beverly Dr., Beverly Hills, Calif.
Place: Los Angeles County Medical Association Bldg., 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn 16.
Secretary: Dr. Jacob J. Lichterman, 1433 Union St., Brooklyn 13.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2032 Belmont Rd. N.W., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S. E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N.W. Time: Spring and fall.

Memphis Pediatric Society

President: Dr. C. Barton Etter, 1678 Peach, Memphis 12, Tenn.
Secretary-Treasurer: Dr. Jacob Danciger, 188 S. Bellevue Blvd., Memphis 4, Tenn.
Place: University Center, 4 S. Dunlap. Time: 7 p. m., second Tuesday of every month.

Milwaukee Pediatric Society

President: Dr. James Conway, 1721 E. Lake Bluff Blvd., Milwaukee 11, Wis.
Secretary-Treasurer: Dr. Walter Polacheck, 425 E. Wisconsin Ave., Milwaukee 2, Wis.
Place: City Club of Milwaukee. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section on Pediatrics

Chairman: Dr. John Dorsey Craig, 120 E. 75th St., New York 21.
Secretary: Dr. Morris Greenberg, 143 W. 87th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. Bertha M. Levy, 717 N. W. 22d St., Oklahoma City 3.
Secretary: Dr. C. M. Bielstein, 301 N. W. 12th St., Oklahoma City 3.
Place: Oklahoma Club. Time: On call.

Philadelphia Pediatric Society

President: Dr. Milton Rapoport, 741 S. 3d St., Philadelphia.
Secretary: Dr. D. Stewart Polk, W. Montgomery Ave., Rosemont, Pa.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday from October to May, inclusive.

Pittsburgh Pediatric Society

President: Dr. J. A. Gilmartin, 3708–15th Ave., Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Municipal Hospital, Pittsburgh. Time: Second Friday in October, December, February and April.

Queens Pediatric Society

Chairman: Dr. Walter C. A. Steffen, 42-28 Union St., Flushing, N. Y.
Secretary-Treasurer: Dr. Louis Appel, 33-03 Parsons Blvd., Flushing, N. Y.
Place: Forest Hills, N. Y. Time: Third Monday of October, February, April; first Monday of December.

Richmond Pediatric Society

President: Dr. Thomas S. Chalkley, 421 W. Grace St., Richmond 20, Va.
Secretary-Treasurer: Dr. John Paul Jones, 810 W. Franklin St., Richmond 20, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Jerome Glaser, 85 San Gabriel Dr., Rochester 10, N. Y.
Secretary-Treasurer: Dr. Daniel B. Peeler, 1162 Lake Ave., Rochester 13, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee.
Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. V. E. Hrdlicka, 7424 Cromwell Dr., St. Louis.
Secretary-Treasurer: Dr. Don L. Thurston, 21 Cambridge Court, St. Louis 22.
Place: Hotel Branscome. Time: Second Thursday of each month from October to May, inclusive, 6:30 p. m.

San Antonio Pediatric Society

President: Dr. Lucius Hill, 328 Medical Arts Bldg., San Antonio 5.
Secretary-Treasurer: Dr. Edith M. Bonnet, 228 Medical Arts Bldg., San Antonio 5.
Place: Bexar County Medical Library. Time: 7:30 p. m., first Tuesday of every month.

Seattle Pediatric Society

President: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle 1.
Secretary: Dr. Jack M. Doctor, 738 Broadway, Seattle 22.
Place: College Club. Time: Fourth Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Harry F. Dietrich, 416 N. Bedford Dr., Beverly Hills, Calif.
Secretary: Dr. Clement H. Maloney, Beverly Hills, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., second Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Ernest H. Watson, University Hospital, Ann Arbor.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. Harry W. Kaessler, 147 Prospect Ave., Mount Vernon, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: The Roger Smith Hotel, White Plains, N. Y. Time: Fourth Thursday of every other month from September to June (dinner meetings).